
COLL. REG. MED. LOND.
MDXVIII
O BIOC
BPAXYC H
ΔE
TEXNH
MAKPH
Alf. Howitsy. Del. et Sculpt
London 1924

THE

COLLECTED PAPERS

OF

SYDNEY RINGER,

M.D., F.R.C.P., F.R.S.

VOL. I.—PAPERS CONTRIBUTED TO THE "JOURNAL OF PHYSIOLOGY."

VOL. II.—PAPERS CONTRIBUTED TO "THE PRACTITIONER."

VOL. III.—CONTRIBUTIONS TO VARIOUS JOURNALS.

ALSO

A LIST OF THE PAPERS AND REFERENCES CONTAINED IN "THE LANCET," AND "BRITISH MEDICAL JOURNAL,"

AND

AN APPRECIATION OF DR. RINGER,
BY BENJAMIN MOORE, M.A., D.SC., M.R.C.S., L.R.C.P.

LONDON:
1912.

CONTENTS.

VOLUME I.

CONTENTS.

VOLUME II.

CONTENTS.

VOLUME III.

Medico-Chirurgical Transactions.

Archives of Medicine.

Medico-Chirurgical Transactions.

ON THE EMPLOYMENT OF GLYCERINE OF TANNIN.

BY SIDNEY RINGER, M.D.

Professor of Therapeutics in University College.

THE writer is induced to make a few remarks on the employment of this preparation of tannin, as it appears to be but little known, and of course but little used, while, in his opinion, it proves of great service in many diseases. He thinks it will be found of great use in ozæna. It not uncommonly happens after measles, or scarlet fever, or other diseases, for the inside of the nose to be excoriated, rather reddened, and to discharge freely a thin sanious, or thicker purulent fluid, which latter, on drying, blocks and scabs up the orifices of the nose; while, often at the same time, from the irritation of the discharge, the upper lip is covered with eczema. If the inside of the nose be well brushed out with glycerine of tannin, the discharge of either kind ceases, often, indeed, after a single application, and the parts heal and become natural again. If the scabs be thick and the orifices blocked up, these crusts must be thoroughly removed, so that the excoriated surface is left bare, which permits the preparation of glycerine to come well in contact with the sore secreting surface.

The obstruction which so generally occurs in the nose of syphilitic children, and which causes in them the characteristic snuffling, may be removed by this treatment. After the application the child breathes much freer through the nose, and then can take the breast much more easily. For while the nose is blocked up the child cannot suck and at the same time take air into the lungs through the mouth, and so it constantly

happens with syphilitic children that they cannot suck properly, in consequence of which they waste away.

Patients constantly apply for relief, who suffer from a chronic discharge from the nose of a thick, lumpy, greenish-black matter, which may continue for years, and which not unfrequently has a most disagreeable smell. Such chronic discharges can very generally be speedily removed by this application ; and even if it continues in spite of this treatment, the offensiveness of the smell is always destroyed. It is necessary that the cavity of the nose should be thoroughly washed out with the preparation.

The treatment is sometimes successful where alum and other injections and washes have failed to affect the disease.

The thin sanious or purulent discharge from the ears so commonly met with in weak, unhealthy children, especially after they have suffered from a severe illness, can be stopped at once by filling up the external meatus with this liquid preparation of tannin. Usually one application is sufficient, but a slight discharge may remain, or it may return again in a few weeks, when it can be again removed by a fresh recourse to the glycerine of tannin. If there be acute inflammation of the meatus, it need scarcely be said this treatment is inapplicable until the acute affection has subsided and become chronic. The chronic vaginitis of children, with thick purulent discharge, can often be at once arrested, by painting the affected parts with this application ; it, however, not unfrequently proves more obstinate than either of the previously mentioned diseases.

This preparation is also of very great use in many cases of eczema. It is of service only in the earlier stages of the disease. Thus, when the skin is inflamed, red, swollen, and weeping, if the scabs be thoroughly removed, and the raw surface be painted over with this preparation of tannin, the discharge is stayed, the redness, heat, and swelling much lessened or removed, and the appearance of the parts much improved. When in a less active condition, and when the tissues are less red, swollen, and weeping, the eczema may more profitably be treated in the same way. The tissues assume a much healthier appearance, and after a few applications look like a healthy, healing sore. A poultice may be usefully applied at night, and this glycerine

of tannin twice or three times in the day. All the advantages which accrue from its employment in this disease have not yet been mentioned, for the troublesome itching, and tingling, and burning so common in eczema, are at once removed by this application, and thus the tearing with the nails and rubbing with the hands which prevents the healing of the sore, and causes it even to spread, is prevented, and the comfort and well-doing of the patient much promoted, as the itching and feeling of burning often greatly break the sleep. Sometimes the glycerine of tannin does not, of itself, quite remove the disease, but brings it to the stage where there is only a little desquamation, with a tendency to crack and ooze. It may be necessary in such case to perfect the cure by a resort to tar or carbolic acid ointment. It need not be said that some cases prove incurable by this as by all other treatment. Impetigo may be beneficially treated in the same way. The scabs should be removed by a poultice applied each night, while this tannin preparation is employed during the day. In the treatment of these diseases of the skin by this application, the state of the digestive organs must not be overlooked, but anything wrong with them should, if possible, be removed.

The eczema which occurs behind the ears of children, and is often limited to these places, is most admirably treated with the remedy. It almost always dries up and heals after one or two applications, even when it has lasted for weeks or months. The gums, if red and swollen, should be lanced, or other irritations removed. Intertrigo of children may also be treated in this way.

It is an extremely useful application to the throat for a variety of purposes. It may be employed with great benefit to the throat when an acute inflammation has just subsided, as the mucous membrane becomes less red, less swollen, and moister, and is covered with mucus or pus. If the glycerine of tannin be then painted on the pharynx, &c. the recovery to their natural state is much hastened, and the chronic inflammation, with a relaxed condition of the mucous membrane, which sometimes follows the acute disease, is prevented. The superficial ulceration which may occur just as the acute conditions are subsiding, may be speedily healed by this application.

In chronic inflammation of the throat, when the mucous membrane is relaxed, moist, and granular-looking, or bathed with mucus or pus, the tissues may be speedily braced up, and these conditions removed, by a few applications of the preparation of which we are speaking, while the hoarseness which may accompany it is at the same time much lessened or removed. Such a throat is commonly met with in children, and is a cause in them of a frequent hacking cough, which may keep them awake for the greater part of the night. A speedy way to cure such a cough is to wash the throat with this astringent application.

Such a state of throat frequently causes slight deafness, a circumstance very common with children, and which may be removed with the chronic inflammation of the pharynx, by the employment of the glycerine of tannin.

It is well known that coughs are often dependent on the state of the throat. But while in theory this fact is very generally accepted, in practice it is very little applied.

In phthisis a frequent hacking cough is often dependent on the state of the throat, and can be allayed by this application. A good night's rest may be obtained by applying the paint just before going to sleep. A small quantity of morphia added to the glycerine of tannin still further increases its soothing sedative power on the throat. The paroxysms of hooping cough may be most considerably lessened in frequency and violence by well sponging out the pharynx with this application; it should be carried low down, and be brought well in contact with the epiglottis and the neighbouring parts.

Its employment will be followed by no good results if the case be complicated with catarrh or other inflammation of the lung, or if there be present tuberculosis or other condition causing fever, or any irritation, as of teething. But in simple uncomplicated hooping cough this application may be used with decided advantage. The paroxysmal cough which is often left behind by hooping cough, or which speedily returns on exposure to cold, may be well treated in this way.

This application has the further advantage of causing no pain, and of not possessing a bad taste. It may be thought an apology is needed for occupying valuable space with the treat-

ment of such trivial complaints. To this it may be answered, they are very common, often very obstinate, and many of them very unsightly.

The writer believes no apology will be considered necessary by those who give the application a fair trial in the purposes for which it is recommended.

ON THE EMPLOYMENT OF DIGITALIS IN DISEASES OF THE HEART.

BY SYDNEY RINGER, M.D.

The beneficial effects of digitalis on some complaints of the heart are most striking, but still much uncertainty as to the precise diseases which are amenable to this remedy appears to be generally experienced. It is with the hope of removing in some degree this uncertainty that the following paper is written.

Its good effects are most apparent in cardiac dropsy ; but it is not suited to all forms of this disease, for the heart complaint, on which dropsy may depend, is not always of the same kind. Thus the dropsy may be due to dilatation of the ventricles, or to some disease where this is not present. Moreover the dilatation may be limited to the right, or may be most marked in the left ventricle. If on the right side, it may be owing to obstruction to the free passage of the blood, as in the lungs from emphysema and bronchitis, which obstruction causes the right ventricle to become engorged, and so distended that its valves are made incompetent, and tricuspid regurgitation with its consequent, dropsy, results. Or the dilatation may be mainly or entirely limited to the ventricle of the left side, and be due to aortic or mitral disease, or to both. Further, there by no means uncommonly occurs extreme dilatation, with a good deal of hypertrophy of the left ventricle, with a murmur having the characters of a mitral regurgitant one, without the existence of any disease of either the mitral or aortic valves. With all these and some other forms of heart disease extreme general dropsy may occur ; but it is in the highest degree important to recollect that digitalis is not equally capable of doing good in all these different diseases, and that a careful discrimination must be made, or the

employment of this drug will very often lead to great disappointment to the practitioner, and it may be harm to the patient. For digitalis, while able in some forms of heart disease to remove most of the symptoms, even when these are of the gravest character, can accomplish little or nothing in the other forms.

It is now proposed to pass in review those kinds of heart disease which may be benefited by digitalis, and also those which are but little if at all influenced for good by this medicine.

With a patient presenting the following symptoms and physical signs digitalis will be found of eminent use. There is present dropsy, which may be extensive; the breathing is much distressed, in the earlier stages of this disease only periodically, and is so especially at night; but when the disease is at its worst it is continuously bad, although it becomes paroxysmally worse. The patient cannot lie down in bed,[1] and is perhaps obliged to sit in a chair with the head either thrown back, or more rarely leaning forward on the bed or some other support. The jugular veins are distended and may feel sore, and the face is dusky and livid. The pulse is very frequent, feeble, fluttering, and irregular. The urine is very scanty, high-coloured, and deposits copiously on cooling. The heart is seen and felt to beat over a too extensive area; and the chief impulse is sometimes at one spot of the chest and sometimes at another. The impulse is undulating, and the beating very irregular and intermittent. The physical examination betrays great dilatation of the left ventricle, with often a not inconsiderable amount of hypertrophy. There is mostly heard a murmur, having the characters of one produced by mitral regurgitant disease, and there may also be disease of the aortic valves.

A case presenting these symptoms and physical signs will very generally respond quickly to digitalis, if given in the fol-

[1] These patients, and also those who suffer from much oppression of the breathing from other diseases of the heart, are often, on account of the dyspnœa, unable to sleep, and in consequence they become much exhausted and wearied out. By the hypodermic injection of small quantities of morphia (one-sixth or one-twelfth of a grain) the dyspnœa may be much quieted, and sleep more or less refreshing obtained. This treatment may be adopted without fear of any disagreeable consequences. Since this foot-note was written Dr. Allbutt has recommended in the *Practitioner* this treatment, which has been long employed by the author and many others.

lowing way. In all treatment, the object must be to obtain the greatest therapeutic effects with the smallest possible dose of medicine. This is particularly important with a powerful drug like digitalis; for if a large quantity be at once employed, it often appears to increase the embarrassment of the heart, and relief will only be obtained when the dose is diminished. And further, it is important not to give a larger quantity of the medicine than is necessary, as it is very possible the patient may require its use for a long period; for in such a case as above described, after a time the patient becomes accustomed to the medicine, and the dose which at first did good seems to have partially lost its effect when a larger quantity is required; but this could only be given with the greatest caution, and even with some danger, if the maximum quantity had in the first instance been employed. The importance of these remarks will be the greater if it should prove, as has been asserted, that digitalis is a cumulative poison. It is further important to keep the dose of digitalis as small as possible, or sometimes, after the medicine has been continued for some time, it produces general convulsions, which generally end in death.

The form of the preparation has, the writer believes, much to do with the success of the drug. The infusion, fresh and well made, will generally give far better results than the tincture. It is advisable to begin by using a drachm of the infusion twice, or not more than three times, a day. In many instances this will be enough. The effects on the pulse, the urine, and dropsy, are to be carefully watched. Under the influence of this medicine, when it is in sufficient quantities and does good, the pulse grows much stronger, more regular, and much slower, till, in very many cases, all irregularity ceases, and it becomes natural in frequency and rhythm. At the same time the urine, which previously may have been not more than half a pint in the twenty-four hours, is increased to one, two, four, or even eight pints a day. With this increase, and in proportion to it, the dropsy diminishes till it disappears. Should the influence of the drug be small or unnoticeable, the quantity in a few days may be increased; but it must be remembered, the good effects of digitalis may not become apparent till three or four days have elapsed. If an increase of the infusion be required, then a

drachm may be given every three or four hours, as the circumstances indicate, or one drachm may be given in the morning, and two in the middle of the day, and two at night. Should the symptoms resist this additional dose, another increase must be made in a few days. It not uncommonly happens that a small dose at first admirably succeeds, and removes much of the dropsy, but fails to accomplish all that is desired; when an increase in the quantity of the medicine must gradually be made.

The cases which we are now treating of require in most instances the free administration of alcoholic stimulants, and the best of these, on account of its diuretic action, is gin.

When a patient with the above-mentioned symptoms dies, there is found at the post-mortem examination great dilatation of the left ventricles, with very generally much true hypertrophy of its walls. Sometimes there is incompetence of the aortic or mitral valves, or of both; but by no means uncommonly both these sets of valves are healthy, and admit of no regurgitation when tested with water, although there has existed, during life, a murmur having the characters of a mitral one.

Digitalis will be found especially useful when there is much dilatation and hypertrophy of the left ventricle without any valvular disease, although a mitral murmur may have been heard during life; but unfortunately it is at present impossible in many cases to decide before death whether there is mitral disease or not.

It has been asserted, by eminent authorities, that if there be aortic disease digitalis is worse than useless, and will embarrass still further the heart, and increase the difficulty of breathing; but after a prolonged and careful investigation of this question the author is convinced that, in a case presenting the physical signs and symptoms above enumerated, the existence of aortic disease, whether obstructive or regurgitant in character, or both, does not in any degree contra-indicate the employment of digitalis.

Of the indications for digitalis above mentioned, the irregularity of the pulse is the most important, and is the one which most decidedly calls for this medicine.

Earlier stages of the above disease are not unfrequently met

with, when the symptoms, though troublesome, are not yet very severe. In these forms it is not uncommonly seen in children who some time previous have had rheumatic fever. In such patients the heart gives evidence of great dilatation and hypertrophy of the left ventricle, whose impulse is strong and heaving. There is generally a systolic apex murmur (mitral), with perhaps systolic apex thrill. At first these patients are only troubled with palpitation or exertion, but after a variable time, it may not be till many years have elapsed, there occur paroxysms of palpitation accompanied by urgent dyspnœa, and so often repeated, it may be, that the child cannot lie down at night, and is obliged to be propped up with pillows. In a further stage of the complaint the dyspnœa is continuous, but becomes paroxysmally worse, and the child is unable both night and day to assume a horizontal position. The pulse is generally in all these stages of the disease quite regular, but is generally very frequent and feeble, although the heart at the same time throbs violently against the chest. There is no dropsy, or this is slight and transient, appearing for a few days and then leaving, till for some reason the heart becomes more embarrassed again.

All these symptoms may be speedily removed, and the comfort and general well-being of the patient in consequence greatly increased, by digitalis. Under its influence the tumultuous strongly beating heart grows quiet and contracts less forcibly, while at the same time the pulse grows less frequent and much stronger.

The circumstance, which may be frequently witnessed, that in cases such as have just been described the pulse may be very weak and feeble, while the heart contracts with unnatural strength, is of importance and is worthy of attention, as is also the circumstance that while the digitalis strengthens the pulse it subdues the unnatural force of the heart's beat.

The first of these circumstances is of importance, as it is commonly concluded, in the cases now treated of, that the weak pulse indicates a correspondingly weak heart, and hence it has been concluded that, as digitalis is eminently suited for these cases, it is useful when the heart is feeble. Such a conclusion is certainly erroneous; for, as has been said, while the pulse is very weak the heart can be felt to strike the chest with a very consi-

derably increased force; and further, when these patients die the left ventricle is found, very considerably dilated, it is true, but also very considerably hypertrophied.

This want of correspondence between the strength of the pulse and the heart's contractions becomes still more apparent when these patients are seized with an attack of palpitation The heart then sometimes beats with sufficient strength to make its movements visible through the clothes, or even to shake the bed, and yet at the same time the pulse is felt to be very small and feeble. Where this discrepancy between the vigour of the heart's contractions and the strength of the pulse is permanent, it would appear as though the patients were troubled with a perpetual palpitation, which, however, becomes paroxysmally worse. This discrepancy between the pulse and the heart, which may be seen as a form of irregularity on the part of the heart, digitalis can correct; and hence, while the heart under its influence becomes quieter and less forcible in its action, the pulse grows stronger as well as slower, and we have an instance in which digitalis controls a too strongly contracting heart.

In older people, an early stage of the severe disease which has been depicted may also be witnessed. In such there is much irregularity of the heart's action, and the pulse is also irregular and intermittent. On auscultation a mitral murmur may very generally be detected, and there is also perhaps an apex systolic thrill. These people may suffer from constant dyspnœa and from attacks of palpitation, during which the embarrassment of the breathing is much aggravated. There is no dropsy nor lividity of the skin, and the urine is secreted in natural quantity. In such a case infusion of digitalis in drachm doses, repeated, once, twice, or three times a day, will give most complete relief, quieting the palpitations, removing the dyspnœa, and regulating the pulse.

If in any of the milder (as also in the severer) forms of these complaints aortic valvular disease be present, such a circumstance is not to be considered an indication against the administration of digitalis.

It is an important question, for how long a time can the digitalis afford relief and preserve life? As might be expected, the good results obtained will depend on the degree to which the

disease has advanced. In its earlier stages the relief may be so complete as to permit the discontinuance of the medicine, and the patient remain relieved for months or many years; but there generally occur occasional returns of the symptoms, which may be again and again removed by a fresh recourse to digitalis. Thus life may be greatly prolonged and made useful, although the sufferer is unfit for very arduous work. Even when dropsy has appeared, and has become extensive, great and permanent relief may sometimes be obtained; but in most cases where the disease has much advanced, and has lasted for some time, the relief—although it may be very great, and all the dropsy and dyspnœa may be removed—is of short duration, and the disease, as it were, catches up the medicine, and progresses in spite of it, till it ends in death. It must be received as a bad sign if a considerable dose of the medicine is required before relief is obtained, as also when it is necessary to give the medicine in increasing doses to maintain the good effects at first obtained.

Before the remarks on this form of heart disease are concluded, it may be mentioned that if no dropsy be present the digitalis will not considerably increase the quantity of urine, and will not therefore act as a diuretic; for usually where there is no dropsy the urine is excreted in natural quantities.

The following appears to be the history of the progress of the disease above described. At first, from valvular disease, or from some at present unexplained cause, the left ventricle dilates, and as it dilates also hypertrophies. When the dilatation and hypertrophy have progressed in some degree, the heart's impulse becomes strong and heaving, and is felt over an extensive area of the chest, while the patient is afflicted, at first on exertion only, with attacks of palpitation and dyspnœa. Next, as the disease advances, either gradually or suddenly, from some cause, the impulse becomes still stronger, more extensive, and more heaving, and the contractions are very frequent. At the same time the breathing is permanently difficult, but becomes with each attack of palpitation paroxysmally worse—so bad, indeed, as to give rise to the idea that the patient cannot live through it.

The pulse in this stage is frequent, small, and weak, and in

strength is altogether out of proportion to the strongly contracting, heaving, tumultuously acting, left ventricle.[1]

As the disease still further increases, there is added to the above symptoms irregularity of the heart's action and irregularity of the pulse. With all the above symptoms and physical signs, there is at first neither fulness nor pulsation of the jugular veins, nor any lividity of the face, nor is there any dropsy; but with the further advance of the complaint these symptoms arise, and are probably produced in the following way.

In consequence of the irregular action of the walls of the heart and its columnæ carneæ, the mitral valves become incompetent, and permit of regurgitation. There may also be disease and incompetency of the mitral valves, with permanent regurgitation from the ventricle to the auricle, which regurgitation will be increased by the irregular action of the heart. By this regurgitation there is offered considerable obstruction to the passage of the blood through the lungs, and hence the right side of the heart is distended, and its valves in their lieu become incompetent, leading to regurgitation back into the veins, and to general dropsy, with lividity of the skin.

When the disease has reached its worst stage, the heart's action is so embarrassed that, although its walls are hypertrophied, it strikes with each beat feebly against the chest, and its impulse may be scarcely perceptible.[2] The pulse is also frequent, feeble, irregular, and intermittent.

In some cases, and especially with children, the disease may advance to a great degree without the occurrence of any irregularity of the heart's action, but with other patients such irregularity occurs early in the complaint.

At the post-mortem examination, and on such examinations these statements are founded, the left ventricle is found, as has already been stated, very considerably dilated, and also very greatly hypertrophied. Often the mitral, and not unfrequently the aortic valves are in a greater or less degree diseased, and admit of a variable amount of regurgitation.

[1] Digitalis controls this too strong action of the left ventricle, and then affords an instance of its usefulness in a hypertrophied and too powerfully acting heart.

[2] Digitalis in such a case quiets the heart, removes the embarrassment, and strengthens very considerably each beat. This is an instance in which the medicine strengthens the beats of an apparently weak heart.

With such a heart digitalis will be found of great service. The following explanation of its action is suggested.

By restoring order to the heart's movements, the regurgitation which was caused by the irregular action of the columnæ corneæ is removed, and regurgitation from the left ventricle to the auricle, and thence through the lungs to the right side of the heart, is prevented. If such be the explanation of its action, then it will only remove with completeness the symptoms when the mitral regurgitation is of the dynamic character, and will not be able to remove those which depend on organic disease of the mitral valves. Such, indeed, is the case; and where, as frequently happens, there exists, in addition to irregularity of the heart's action, organic disease of the mitral valves admitting of regurgitation, the digitalis, by removing the former, will remove the dropsy and other symptoms which it produced, but will leave the dropsy, and that share of the symptoms dependent on the organic disease of the valves, unaffected.

The truth of this statement may be verified, as such cases as the following kind unfortunately too often occur. A patient with dropsy, and with symptoms and physical signs like those above described, is partially benefited by digitalis, and much of the dropsy and dyspnœa is removed, but the medicine is unable to afford complete relief. After death there is found much disease of the mitral valve which permitted of regurgitation, and the left auricle is in consequence much distended. Such a condition of the mitral valves the digitalis of course could not remove, but that share of the dropsy and other symptoms which were produced by the irregular action of the heart, the digitalis was able to remove. The truth of these statements may be abundantly verified by post-mortem examination, combined by clinical observation, which investigations will show that digitalis is useful in proportion to the degree in which the dropsy, &c., is due to irregular action of the heart, and is independent of organic disease of the mitral valves.

Cases of the following kind not uncommonly occur, which may be greatly benefited by digitalis.

A patient (who has been perhaps troubled with slight palpitation of the heart for some years) on catching a cold is attacked with bronchitis, and has, in consequence, the palpitations much

increased. These palpitations in their turn excite severe paroxysms of dyspnœa. On examination the heart may appear healthy, or there may be only a slight mitral murmur. Such persons may have the palpitations removed from them, and the breathing made calm, by digitalis.

This medicine, however, leaves the bronchitis untouched, except that, by easing the breathing, it indirectly assists expectoration, and enables, by the same means, the patient to obtain refreshing sleep. In this indirect way digitalis may benefit the bronchitis, but the medicine here acts on the heart; and if with bronchitis there occurs much palpitation or irregularity of the pulse, this remedy is indicated.[1]

Before treating the paroxysmal dyspnœa which may be present with bronchitis, it is important to learn if the paroxysms are accompanied by, and depend on, palpitation of the heart; for if so, ordinary antispasmodics, as lobelia, chloroform, or ether, will be without avail. Digitalis is the remedy generally required, and a drachm of the infusion taken twice or three times a day is generally sufficient.

Functional palpitations, and those attacks of palpitation which occur with hypertrophy of the heart,[2] may be relieved by small doses of digitalis. Here, probably, the palpitations are owing to some temporary aberration of function which the digitalis can set aside. It is certainly wrong to view the palpitations as the result of too much healthy action.

Those forms of heart disease which may produce dropsy, but over which digitalis has little or no control, will next be spoken of.

General dropsy dependent on heart disease is in some instances produced in the following way. The lungs degenerate and become emphysematous, and hence offer obstruction to the free circulation of the blood from the right to the left side of the heart. To meet and overcome this obstruction the right ventricle grows hypertrophied, but only sufficiently so to meet the obstruction offered to the circulation; and there is, unlike the healthy heart, but little reserve power left in this organ, and hence, on the occurrence of any sudden access to the obstruction of the circulation

[1] If during a fit of palpitation the heart beats very violently, one or two drops of tincture of aconite, given every quarter of an hour, may succeed in quieting it better than digitalis.

[2] Aconite is very valuable in such cases.

through the lungs, the right ventricle becomes unequal to the task thrust upon it. Such a sudden access of obstruction is occasionally bronchitis; and on the occurrence, therefore, of an attack of this disease, the blood, unable to pass through the lungs with sufficient ease, accumulates in the right cavities of the heart, and overloads them to distension, till the tricuspid valves become incompetent, and permit of regurgitation from the ventricle to the auricle, and thence into the veins, where, if the obstruction in the lungs be great, dropsy will ensue. In such cases the dropsy varies with the amount of bronchitis; as this increases or declines, so does the dropsy grow greater or less. If the distension of the right cavities lasts a considerable time, then, on the disappearance of the bronchitis, the cavities do not regain their natural size, and the tricuspid incompetency becomes permanent, and the dropsy also.

In such a disease, digitalis appears to possess very slight if any power to strengthen the heart to overcome the obstruction in the lungs, and in consequence it is without any good influence unless the heart acts irregularly, which irregularity, when at all extreme, and even without either hypertrophy or dilatation of the left heart, or disease of its valves, adds to the difficulty of the breathing, diminishes the quantity of urine, and produces dropsy, or increases it if it is already present from the obstruction in the lungs. Such irregularity digitalis can remove, and with its removal will disappear that excess of the symptoms which it produced.

The inability of digitalis to strengthen the heart, and thus enable it to overcome any obstruction offered in the lungs, is well shown in cases of the following kind. A patient of middle or advanced age, whose heart is much dilated on the left side, and which acts irregularly, has in consequence suffered from dropsy, dyspnœa, &c., which effects have been thoroughly removed by digitalis. On catching cold, and on the occurrence of bronchitis, the dyspnœa, lividity, dropsy, &c., return, and it would naturally be thought that digitalis, which had previously done so much good by removing the same symptoms, would be again of service. But such is not necessarily the case, and a nice discrimination of the circumstances producing the return of dropsy, &c., must be made. Such a return, if there is much emphysema of the lungs, is not uncommonly solely due to the

obstruction caused in the lungs by the bronchitis and emphysema, and is in no way dependent on any effect the bronchitis has produced on the dilated left ventricle. In such a case digitalis can do no good, but remedies possessed of the power to control the bronchitis are needed. If, however, as not uncommon, the bronchitis affects the dilated left ventricle, and brings back the conditions which were present when the digitalis did so much good, then a return to this medicine will again afford relief. In deciding the question whether digitalis should be given or not, attention must be directed to the following points. If on the return of the dropsy, &c., there is also excited fits of palpitation, and with these also attacks of dyspnœa, and if also the heart be made to beat irregularly, digitalis is required ; but if, on the other hand, although there is hurried breathing and a very quick pulse, the symptoms just mentioned are absent, the patient will obtain no good from digitalis.

There are other serious diseases of the heart by which dropsy may be produced, but over which digitalis has no control, and in which, unless care is taken, it may do much harm. The following is a concise description of such cases.

The patient, often in the prime of life, and it may be without any history of rheumatic fever, has for some time, perhaps for many years, suffered on exertion from palpitation. On auscultation there is heard an aortic, obstructive, or regurgitant murmur, or both combined. The heart is hypertrophied to overcome the obstruction to the circulation occasioned by the aortic valvular disease, and by this compensation the patient is saved from any troublesome symptoms except some palpitations. After a variable time serious symptoms may arise, which generally rapidly increase in severity, and in the course of a few weeks or months the patient dies. On this aggravation of the disease there occur paroxysms of palpitation, accompanied by urgent dyspnœa, which attacks may be occasioned by the slightest exertion, but also occur without any such provocation. Soon the dyspnœa becomes constant as well as paroxysmal, and about this time there appears dropsy in the legs, which rapidly extends till it invades the greater part of the body, and is often in excess in the pleural or peritoneal cavities. During the whole progress, and to the termination of the disease in death, *both the heart and pulse beat regularly and without any intermissions,* and the latter has often

the characters which are significant of aortic regurgitant disease. There is no lividity of the skin, but on the contrary this is strikingly pale and waxy looking; neither is there any fulness or regurgitation into the jugular veins. In addition to the aortic murmurs there may be one having the character of mitral regurgitation, but after death these valves are generally found healthy and competent.

The following appears to be the pathological history of such patients. On the occurrence from any cause of disease of the aortic valves the left ventricle grows hypertrophied, and is thus enabled to overcome the obstacle offered to the circulation by the valvular affection; and while the hypertrophy keeps pace with the disease, the patient is only troubled by the increased action of the hypertrophied heart, and in this condition the patient may live for many years but little incapacitated for work. After continuing in this state for a variable time, the disease of the heart may produce serious and fatal symptoms in the following ways, in both of which the effect on the circulation is the same. In the one case the disease in the aortic valves advances with great rapidity, so quickly indeed as to make it impossible for the left ventricle to hypertrophy sufficiently to meet the obstruction to the circulation offered by the aortic disease. In consequence much derangement of the circulation ensues, on which the serious symptoms above detailed depend.

In the other case the disease of the aortic valves may remain stationary, or progress very slowly, but the hypertrophied left ventricle undergoes (sometimes with great rapidity) degeneration, and becomes much softened, and in consequence of these changes in its structure it loses much of its power, and is unable to meet the increased demand made upon it in consequence of the disease of the aortic valves, and hence is produced a disturbance of the circulation similar to that of the former case, and there then arises the dyspnœa, palpitations, &c., which have been described.

In such cases digitalis will do little or no good; it sometimes appears to control in a slight degree the palpitations and the attacks of dyspnœa, but it not unfrequently happens that under its influence the pulse grows feeble and intermittent, an effect the author has witnessed when the substance of the left ventricle was much degenerated and softened.

THE PRACTITIONER.

MARCH, 1872.

Original Communications.

PURPURIC SPOTS PRODUCED BY IODIDE OF POTASSIUM AND IODIDE OF AMMONIUM, BUT NOT BY IODIDE OF SODIUM.

BY SYDNEY RINGER, M.D.

It is well known that iodide of potassium occasionally produces a petechial rash, limited generally, as in the following case, to the legs. A case of this kind occurring in University College Hospital, it was considered a good opportunity to learn whether other iodides act in a similar manner in an equal degree.

These observations were made by Mr. Nankevell, one of the resident medical officers of University College, on a lad aged 17, convalescent from acute rheumatism, and free from fever, to whom was given for a few lingering pains iodide of potassium in ten grain doses, thrice daily.

He began the iodide of potassium on December 4th, and on December 9th a petechial rash broke out on the front and sides of his legs and ankles. The spots were numerous and varied in size from a pin's head to a split pea. Neither on this or any subsequent occasion did any spots appear on any part of the body above the knees. Rather sharp blows over the shins did not bruise. The shins were a little tender. Slight coryza pre-

ceded the spots by a few days. The medicine was discontinued on the morning of the 10th, and by the 15th the spots disappeared. On the 18th he began again the medicine, and on the morning of the 20th, *i.e. after four doses*, the rash reappeared more abundantly than at first, and coryza set in the same evening. The medicine was again discontinued, and by the 26th the rash disappeared; on which day he recommenced the medicine, and by the 28th, *after five doses*, the petechial rash again appeared. The medicine was discontinued, and the rash disappeared on January 1st.

On January 4th the lad began iodide of ammonium, in ten grain doses; after two doses, and in six hours and a half, petechial spots broke out on both legs. He took a third dose, and then the medicine was discontinued, and the spots disappeared on the 9th. He was then ordered iodide of sodium, but owing to a mistake a mixture containing iodide of ammonium and iodide of sodium, each in ten grain doses, was prepared. Of this mixture he took one dose before the detection of the mistake. Afterwards he took iodide of sodium in ten grain doses. On the same night, after two doses of medicine, *i.e.* after ten grains of iodide of ammonium and twenty grains of iodide of sodium, the petechial rash appeared.

On the 15th, the spots having disappeared, the lad began iodide of sodium in ten grain doses, to be repeated three times daily. He continued the medicine till mid-day of the 19th without the appearance of any petechiæ or coryza. At 3 P.M. of that day he began iodide of ammonium in ten grain doses, and at 5 P.M., *i.e.* in two hours, a few spots were visible on both legs. The spots were more numerous and more marked next day.

The iodides of potassium and ammonium produced no other effects than the petechial rash and coryza, neither increasing the pulse nor raising the temperature nor producing the characteristic rash, nor any feeling of weakness.

No doubt it would have been more satisfactory if the iodide of sodium had been given for a longer time and in larger doses, in order to show more conclusively whether the effect of the iodide of sodium differed merely in degree from that of other iodides.

ON THE INFLUENCE OF BELLADONNA ON SWEATING.

BY SYDNEY RINGER, M.D.

THE remarkable influence of belladonna applied to the breast in checking the secretion of milk, led the writer to try its influence on sweating. He first employed belladonna in a case of unilateral sweating. A man, forty-five years old, had been troubled for many months with very profuse sweating of the right side of the face and neck, breaking out on the slightest exertion or excitement, or when near a fire, so that the sweat ran down his face and neck in streams, soaking his collar and the band of his shirt, his face being neither red nor congested. The perspiration produced an abundant crop of miliary vesicles, which were strictly limited to one half of his face. The liniment of belladonna applied two or three times a day abated this copious sweating considerably, and reduced it to a little more than the natural amount, and this improvement lasted about six months after the discontinuance of the application, and then the sweating gradually returned, till it became as bad as ever.

The writer has many times checked the sweating of the head and face of young children, often so profuse as to soak their hair and the pillow on which they have been sleeping. Again, belladonna, by means of the ointment or liniment rubbed in two or three times a day, he has several times checked the profuse sweating of the hands, which is sometimes so copious as to run off them in drops, and is especially noticeable at the finger-tips and thumb-balls. Sometimes the good effects are permanent, sometimes the sweating may not return for a considerable time; but occasionally, however, this treatment fails.

The following curious case of unilateral sweating illustrates the beneficial effects of belladonna:—Mrs. P——, aged thirty, married, has all her life sweated freely, but much more on the left than on the right side of her body, the excess being most marked on the head and trunk, although the left arm and leg sweat more than the right. The line of demarcation on the face is sharply defined, equally dividing the head down the centre. The sweating on the left side is very profuse, running down her face and soaking her hair and even the bed-pillow. The sweating on the left side of the trunk is most marked, as low as the breast. Slight exercise, sleeping, or exposure to the heat of the fire or sun, especially the latter, greatly augments the sweating. It is markedly profuse when she is out of health. The sweating is unaccompanied by flushing, and does not excite any rash. She suffers from great coldness of the feet, but the right foot is decidedly the colder. She never feels the left hand warmer than the right. The left side of her tongue is always more coated than the right, and has been so as long as she can recollect. There are no bad teeth or other causes in the mouth to account for this curious fact. She is rather deaf on the left side, and when young was very deaf of both ears, but much worse on the left side. Her pupils are equal, and her sight good in both eyes. She is very hysterical, and suffers often from globus hystericus, and from a sensation of heat and weight on the top of her head and palpitation on exertion or excitement. Her urine varies greatly in quantity, sometimes being scanty, at other times very abundant. Her bowels are generally confined, and she is troubled with a cankery taste in the morning. Her menses are very scanty and irregular, intermitting sometimes for six months. She does not blush more one side of the face than the other; and when excited her ears become both equally very red. The skin of the face presents the same aspect on each side. The radial pulses appear to beat in all respects equally. Five months ago she was confined, and since then all her troubles have much increased. The left breast yields much less milk than the right, this being full and distended, while the left is flat and empty. Shortly before her visit to the hospital she was seized with neuralgia of the auriculo-temporal branch of the inferior division of the fifth nerve on the left side, the paroxysm being accom-

panied by salivation of the left side of the mouth ; but previous to this neuralgic attack the secretion of saliva was no greater on one side of the mouth than on the other. During an attack of pain the left side of the face sweated greatly.

She has lost two children—one from measles, the other from hemiplegia. Deafness is a family complaint; no other member of her family suffer from nervous disease, and none are affected with unilateral sweating. At fourteen years of age she suffered for a year with twitchings of the right side, the arm being especially affected, but this does not appear to have been true chorea : and still on excitement there is a disposition to involuntary movements of the right arm.

The application of a weak belladonna ointment to the left side of the face for five to ten minutes, three times daily, greatly reduced the sweating and equalised that of the two sides. It moreover cured the neuralgia.

The author has met with cases of profuse local sweating over the loins, covering a surface rather larger than the hand, and exciting a copious eruption of eczema. Here the belladonna liniment checked the sweating, and the eczema at once disappeared.

In some cases of sweating the belladonna no doubt fails. Thus in one inveterate instance, so far from affording relief, it increased the sufferings and sweating in the case of a man who for twenty-two years had been affected with an occasional eruption of the hands and feet, looking at times like eczema, but at other times putting on the appearance of lichen. In cold weather he is pretty well, unless he takes exercise or sits in a hot room ; but in March, as the weather begins to get warm, the symptoms set in. His hands and feet swell and feel so tight as if they must burst. At the same time he sweats a good deal, but not while lying down ; but directly he rises, or even sits, the sweating begins. The sweating is much more abundant in his hands and feet, especially at the finger-tips and the thumb-balls; and at the tips of the ring and little fingers of the left hand it is especially marked. The sweat runs down in drops from the hands, and when he wipes the finger-tips he can see the sweat oozing from the pores of the skin. The outer part of his hands corresponding to the fifth metacarpal bone is also the seat of great sweating. At the tips of his fingers and the thumb-balls he suffers from severe

pricking pain, which he likens to little insects biting their way out. He feels hot all over, and calls it heat in the blood. The attacks are accompanied by a good deal of itching over his back. The skin of the hands about the nails becomes hard, cracks, and bleeds. A little rash similar to that described appears in the clefts of the fingers and over the back of the hand between the thumb and fore-finger. In this patient's case, as has been stated, belladonna ointment applied to the hands greatly aggravated all his troubles and increased the sweating.

In order to test still further the effects of belladonna on sweating, many experiments of the following kind were performed by Mr. C. A. Nankivell on several occasions:—A patient in University College Hospital, after undergoing a sweating in the hot-air bath, was rubbed with belladonna ointment on one side of the face for ten minutes, three times a day, for two or three days; then the bath was repeated of the same temperature and duration, when it was observed that the sweating both during and subsequent to the bath was very greatly lessened, and that the effect was general, although the ointment was applied only to one side of the face. On some occasions the ointment was rubbed into the chest, but then the effects were much less marked than when applied to the face, possibly because less of the ointment was absorbed.

As the local application checked sweating over the whole body, it was concluded that it acted by its absorption, and this led to the internal administration of belladonna, but its repressing effect was apparently decidedly less than when locally applied, possibly because less of the drug was given by the mouth than was absorbed by the skin. Still, no doubt the internal administration of belladonna does sometimes effectually control sweating, as the author has often witnessed in the case of weakly children perspiring profusely on exertion or whilst sleeping; and in the following curious case of a middle-aged man who, after much mental worry, suffered from excessive sweating of both cheeks while eating, especially hot meat or vinegar, the sweating ceased immediately after the meal. This man passed at times a profuse quantity of pale urine. Ten drops of tincture of belladonna taken three times a day completely checked the sweating.

Since writing the foregoing, the author has made some further experiments with very striking results. A middle-aged man, a sufferer for several years from unilateral sweating of the right side of the face and neck, applied for relief from a pain in his side. He was found to be sweating very profusely from the right side of his face and neck, from exertion and the great heat of the weather. To relieve his pain a twelfth of a grain of morphia was subcutaneously injected, which appeared to increase the sweating, although it was difficult to be sure of this: while still sweating profusely, so that on wiping his face the sweat could be seen rapidly oozing from the skin, we injected $\frac{1}{100}$ of a grain of atropia under the skin of his arm, and in about a minute the sweating entirely ceased, and his face remained quite dry, till his dismissal about three-quarters of an hour after the experiment.

To a middle-aged woman suffering from acute rheumatism, a hot-air bath was administered, followed by cold sponging. This treatment caused her to sweat so freely that for several hours after the perspiration continued to pour down her face, soaking her clothes and the bed-linen. While in this state $\frac{1}{100}$ of a grain of atropia was subcutaneously injected into her arm, and in about a minute the perspiration ceased, and for two hours her skin continued dry and she felt much cooler, but in the evening rather free perspiration returned. We next gave a young man a Turkish bath, and Mr. Johnson, the resident assistant of wards, who has helped me in these observations, joined him in the hot chamber. Both sweated freely, and then each was injected with $\frac{1}{100}$ of a grain of atropia, and in a little more than a minute the skin became dry, and the perspiration did not return after the application of the cold douche, nor afterwards. Mr. Johnson remarked that so dry did his skin seem, that he felt he should never sweat again. They both suffered from much dryness of the mouth, but their pupils were not dilated. We next placed a boy in the hot-air bath, the temperature rising to 180° Fahr., and when sweating freely we injected $\frac{1}{120}$ of a grain of atropia, and almost immediately the sweating ceased and did not return.

A CURIOUS CASE OF FACIAL NEURALGIA WITH UNILATERAL SWEATING CURED BY THE APPLICATION OF ACONITE LINIMENT.

BY SYDNEY RINGER, M.D.

MARY RANCHEN, aged forty-five, applied at University College Hospital on April 26th. Her father died of rheumatic fever; her mother in her third attack of apoplexy; and eight of her mother's sisters of "apoplexy" at the age of twenty-four or twenty-five. One sister died of dropsy, another of paralysis, a brother of convulsions when a few months old. One brother is a healthy man. She has a son aged sixteen, and a daughter thirteen, both healthy, and who never suffered from convulsions. At her last confinement she had twins, who died immediately after their birth. Five years ago the patient was seized with hemiplegia of the left side, affecting the face as well as the arm and leg. The face soon recovered, but the leg did not recover for two years. The arm recovered before the leg. The catamenia ceased about a year ago. She has felt a little pricking pain on the right side of the face for two months, and meanwhile has suffered from unilateral sweating of the right side, and has passed a large quantity of water, to the extent, she says, of six pints a day, and complains of distressing thirst. Unfortunately we could not get any of her urine to search for sugar.

About eight days ago the right nostril began to run freely, and on the 23rd (three days ago) the right eye began to water, and in a few hours she was seized with a very severe pricking pain of the right side of the face. The pain has recurred three

times daily—in the morning, afternoon, and evening—each paroxysm lasting about two hours. She describes the pain as being most severe, and compares it to pricking every part of the skin with a red-hot needle. The pain corresponds to the distribution of the supra-orbital, infra-orbital, and inferior dental branches of the right fifth. The pain reaches exactly the middle line of the nose, but not quite to the middle line of the upper and lower lips. On April 24, the second day of her illness, the right side of her face became greatly swollen, the swelling increasing with each paroxysm, and decreasing shortly afterwards. On the 25th she felt pricking pain inside her nose. On her first visit (26th), the right side of her face was very red and greatly swollen, so that she opened the eye with difficulty. The right eye was greatly injected, and exposure to the light produced great pain. There was great lachrymation, and its vision was greatly impaired. There was a little swelling on the left side, in the neighbourhood of the infra-orbital foramen. The pain which has been described was most severe, and was limited to the right side; the swelling of the left side of the face being free from pain. She complained of severe pricking pain in the right eyeball. The motor branch of the fifth was unaffected. Hearing and taste were natural. The pupils were much contracted, but equal. There was no ptosis, no strabismus, nor paralysis of the seventh or ninth nerves. The right side of her mouth seemed dry to her, although on the left side there appeared to be excess of saliva. After the attack of paralysis she suffered for some time from cold feet, but gradually this symptom got better, but returned with the present attack. The right extremity is very cold as high as the knee, and is colder than the left. The right is so cold that it wakes her, and she is obliged to put on a thick woollen sock and use a warm bottle. The unilateral sweating on the right side reaches only as low as the knee.

On the day of her first visit we painted the right side of her face with aconite liniment, and on the following day (April 27) we found that the pricking pain was very much less severe and more limited, and the right eye was much less bloodshot, less painful, and she could see distinctly. The running at the right nostril was greatly lessened, but the excess of sweating on the right side was undiminished. The aconite liniment gave her

sharp pain like that of a drawing blister, and made the skin quite numb.

On the 29th she stated that, on leaving on the 27th, slight pricking pain returned under her right eye, but on applying the liniment lightly, the pain in ten minutes disappeared. In the afternoon she experienced slight pricking along the right lower jaw, but the liniment lightly applied removed it immediately, and ever since she has been free from pain. To-day (29th) there is no swelling of her face, the right eye is very little bloodshot, and the sight is perfect. She perspires much less, and the sweating of the two sides is equalised. On the first day after the application of the aconite liniment her feet became warm, and have not since been cold.

[I take the liberty to append a few remarks, for which Dr. Ringer is in no way responsible, to this very interesting case. The above narrative appears to me to afford an instance, though a rare one as to degree, of successful treatment by interrupting the conductivity of peripheral nerve-branches. A multitude of circumstances, which it is needless to point out in detail, indicate that the morbid process which really caused the neuralgia in this case was seated in the medulla, involving primarily the centres which belong to the sensitive and vaso-motor fibres of the fifth nerve: but ultimately spreading to other vaso-motor centres. Yet the cure seems to have been produced simply by paralysing the peripheral portion of the fifth nerve, and thus giving the centres rest from the impact of impressions from without.—F. E. ANSTIE.]

SOME ADDITIONAL OBSERVATIONS ON THE ACTION OF ATROPIA ON SWEATING.

BY SYDNEY RINGER.

I MADE these observations, with the assistance of Mr. Johnson and Mr. Curtis, resident officers of University College Hospital, to learn the smallest quantity of atropia injected hypodermically required to check sweating.

We injected $\frac{1}{300}$ of a grain of atropia into the arm of a man aged 60, while he was sweating profusely in the hot chamber of the Turkish bath. In fifteen minutes the sweating became considerably less, but after nineteen minutes the perspiration returned abundantly, but less than before the injection. He perspired freely after the cold needle bath.

We placed a lad in a hot-air bath of 194° Fahr., and when perspiring profusely we injected $\frac{1}{300}$ of a grain of atropia. In five minutes the perspiration was decidedly less, and in ten minutes was very slight, but in thirteen minutes it again became profuse. Then we injected another $\frac{1}{300}$ of a grain, and in two minutes his face became perfectly dry, and remained so during the rest of the *bath*, i.e. ten minutes.

We next injected $\frac{1}{200}$ of a grain into the arm of a lad while sweating profusely in the hot chamber of the Turkish bath. Four minutes after the injection his body was quite dry, but subsequently slight moisture appeared on his forehead. After the cold needle bath, his skin remained perfectly dry.

Our next observations were made on patients troubled with profuse sweating, especially at night. The first patient suffers from a renal tumour, with discharge of pus in her urine. She was free from fever, neither was she very weak. The profuse

sweating caused her great annoyance. On August 30 we injected hypodermically $\frac{1}{100}$ of a grain of atropia. This completely checked the sweating on that and the following night. On Sept. 1 she was sweating again very freely, and $\frac{1}{200}$ of a grain was injected, which effectually prevented the sweating. The sweating, however, returned as freely as ever the following night, but on the four following nights her skin became dry, although this had never occurred previous to the employment of atropia. On the nights of Sept. 8th, 9th, and 10th she sweated as freely as ever. On the 11th, $\frac{1}{200}$ of a grain of atropia was injected, and her skin remained dry during the whole night. The injection made her sleep sounder.

On many occasions we injected $\frac{1}{200}$ of a grain under the skin of a woman suffering from advanced non-febrile phthisis, who sweated very freely on sleeping. On every occasion the atropia completely checked the sweating. Similar observations with $\frac{1}{200}$ of a grain, and with equally satisfactory result, were made on a man with febrile phthisis.

Our observations lead us to conclude that $\frac{1}{200}$ of a grain of atropia, injected hypodermically, is sufficient in most cases to check sweating for one night. Our observations are too few to determine whether after employing the injection on several nights the sweating can be relieved on discontinuing the treatment, but we believe that after a short course of this treatment the injection may be discontinued for a few nights without the return of sweating.

This treatment gave the phthisical patients better sleep, and we think allayed their cough; but unfortunately in most cases it caused very uncomfortable dryness of the throat.

Mr. Johnson assisted me in some experiments with stramonium. We found that, like belladonna, stramonium, subcutaneously injected, will very speedily check sweating, and produce dryness of the mouth. We noticed that while belladonna and stramonium checks sweating, they deeply flushed the face. Hence their influence over sweating cannot be due to their effect on the sympathetic ganglia thereby lessening the supply of blood to the skin, unless they can affect the blood-vessels supplying glands, while they leave unaffected the other vessels.

A CASE OF RHEUMATIC FEVER WITH HIGH TEMPERATURE SUCCESSFULLY TREATED WITH COLD BATHS.

BY SYDNEY RINGER, M.D.

Ellen Hillier, aged 22, was admitted into University College Hospital, Aug. 21, 1872. When four years and a half old she suffered from a severe attack of rheumatic fever, soon followed by a sharp attack of scarlet fever. Since that time she has remained quite well till her present illness, which began about a fortnight before her admission, but she continued at her work till the 18th of August, when severe pain in her knees compelled her to keep her bed.

At the time of her admission she suffered from a rather sharp attack of rheumatic fever; the temperature rising daily to 103°·5 Fahr. On August 22, it is recorded in the note-book that she was free from pain, except on movement, when she complained of her knees. The right knee was excessively tender. She complained of pain over her chest. A soft basic systolic murmur and slight friction were heard. The apex sounds were muffled.

To relieve the pains she was ordered laudanum three times a day. On the 24th of August she came under my care. I saw her at 10 A.M. and found her drowsy, with strongly contracted pupils, due to the opium, which was immediately discontinued. Her temperature was 104°·5. Fearing from the high temperature, her freedom from pain, and dull listless condition (though it was impossible to tell how far these circumstances were due to the disease or to the opium), that the temperature might become excessive, it was agreed that in the event of the fever rising to 106° a cold bath should be administered. At 4 P.M. the thermometer recorded 105°·2 Fahr.; at 11.45 P.M., 105°·6.; at 12.45

(August 26th), 106° ; 1 A.M. (in rectum), 106°·5. At this time she was semi-comatose, delirious, and *sweating profusely*. At 1.20 she was placed in a general bath of 86° Fahr. to which ice was added, so that its temperature was gradually reduced.

Time.	Temp. in rectum.	Pulse.	Respiration.	Temp. of bath.	Remarks.
A.M.					
1.35	104·6	136	22	82	Temperature of room 72° Fahr.
1.50	101·8	123	22	80	
2.5	100·8	120	14	79	Dozed for a minute at a time.
2.20	99	116	20	78	Vomited.
2.22	...	...	...	...	Removed from bath.
2.35	95·2	118	16	...	Temperature taken in mouth.
3	95	110	16	...	
3.15	96·8	114	14	...	,, ,, rectum.
4	96·2 ?	112	12	...	,, ,, axilla.
4.30	98	112	16	...	,, ,, ,,

After being in the bath ten minutes, she complained of the cold, and when put to bed was rather depressed and chilly, so we covered her with warm blankets and placed hot bottles by her side, and gave her half an ounce of brandy, which she soon vomited. The brandy was repeated in three-quarters of an hour and retained. At 4.30 she vomited some brandy given her a short time before. She felt warm and comfortable. Soon after leaving the bath she fell into a quiet light sleep, which, with occasional remission, continued till half-past five.

It thus appears that a bath of 80° Fahr. in an hour's time reduced the temperature 6°·5, and that the temperature subsequently fell, during the following three-quarters of an hour, 2°·2 Fahr.

Time.	Temp. in axilla.	Pulse.	Respiration.	Remarks.
A.M.				
5	98·4	116	16	Feels very comfortable.
5.30	99·3	118	16	Sleeping.
6	100·4	120	16	Took some tea.
7	102·1	124	16	No perspiration. Feels comfortable.
8	103·7	132	24	No sweating.
8.30	104·8	140	28	
9	105	148	24	

The temperature rising thus rapidly, we determined to employ

the cold bath again. At 9.10 she was again immersed in a general bath of 90° Fahr.

Time.	Temp. in axilla.	Pulse.	Respiration.	Temp. of bath.	Remarks.
9.25	103·4	132	32	84	Temperature taken under tongue.
9.38	102	...	...	75	

At 9.40 she shivered so violently, and the pulse growing very weak and her face becoming livid, we removed her from the bath and gave her a little brandy.

Time.	Temp. in axilla.	Pulse.	Respiration.	Remarks.
9.45	101·2	120	28	
10	100·8	116	22	
10.15	101	120	24	Took a cup of tea.
10.30	101·3	112	24	Asleep.
11.15	102·6	124	28	Asleep. Skin hot and dry.
12.15	103·6	128	28	Asleep. Skin pungent, face flushed.
12.45	103·6	140	32	Sweating about face and chest. Three large ice-bags[1] applied,—one between legs, one over abdomen, and the other over chest.
P.M.				
1.15	103	128	32	
2	102·2	120	28	Blankets removed and sheet substituted.
2.30	102·5	112	28	
3	101·8	116	36	
3.30	102	112	32	Four ice-bags applied. Taken food freely.
4	101	112	28	
4.30	100·8	116	32	Chilly hands and feet. Cold ice-bags removed, and patient covered with blankets.
5	100·8	112	24	
5.30	100·6	...	...	
6	101·6	...	...	
6.20	...	120	...	Chilly. Catamenia ceased on 23rd; just reappeared in small quantity. 8 oz. urine passed at 5 P.M., clear acid, sp. gr. 1012; no albumen.
6.30	102·2	...	...	
7	102·4	124	32	Complains greatly of severe pain down sternum to umbilicus. One-sixth grain of morphia hypodermically injected at 7.45.
8	102·8	128	30	Sweating about face. Just woke from half-hour's quiet sleep.
8.30	10	140	24	An ice-bag applied at 8·50, others subsequently applied, and at 9 P.M. a fourth was used.
9.30	101·7	124	24	Feels very comfortable. Slept for half an hour.
10	100·4	122	20	
11	98·4	112	24	Chilly. Ice-bags removed.
12	99	116	16	Very comfortable.

[1] Chapman's large spinal ice-bags.

The temperature slowly rose during the night, and at 6 A.M. (August 26) reached 102°. During this time she slept quietly. At 5 A.M. she passed a clay-coloured stool. At 6.30 four ice-bags re-applied.

Time.	Temp. in axilla.	Pulse.	Respiration.	Remarks.
Aug. 26 A.M.				
6.40	102	...	...	
7.20	101·6	...	...	
8.15	101	...	...	
8.45	101	...	...	
9.15	100·5	...	...	One ice-bag removed.
9.50	100 8	...	...	Chilly.
10.30	101·2	124	25	Passed loose, copious, clay-coloured stool.
11	100·4	120	28	
12	101	120	28	
1	169·8	120	...	
1.20	101	...	...	Only one ice-bag left on, across abdomen.
2.45	101·2	118	30	Sleeping comfortably.
3.30	101	124	...	Chilly. Pain over sternum less severe than yesterday.
4.30	101·2	112	24	
6.20	101	124	28	Ice-bag removed at patient's urgent request.
7.50	101·6	..	...	Violent pain at epigastrium, making patient groan, unrelieved by hot fomentations with opium; one-sixth grain of morphia hypodermically injected.

At 8.20 she was seized with very severe pain over the front of the right side of the chest, and as at 10.15 the pain continued, another injection, one-sixth grain of morphia, was administered hypodermically. After this she passed a quiet night, sleeping well. The temperature was taken hourly through the night, and varied between 100°·5 and 101°·4. At 7 A.M. it was 102°. At this time she complained of much pain on swallowing, but was otherwise free from pain. At 7.30 A.M., August 27, one ice-bag was placed over her abdomen and was continued till 3.45 P.M. without any apparent influence on the temperature, when it was removed.

On examining her chest we found marked dulness on the right side below the fifth interspace, and other signs of pneumonia affecting the right lung. Loud double friction was heard over the whole of the heart region. At noon she complained of severe pain in the right shoulder and right side of the chest,

which yielded to hot poultices with laudanum sprinkled on them; but, the pain returning at half-past three, one-sixth of a grain of morphia was again injected. At 10.30 P.M. the temperature rose to 103°, when two ice-bags were applied—one between her legs, the other over the left side of the chest and across her abdomen. At 12 the temperature was 101°·8, when the ice-bags were removed, and being restless, she took ten grains of chloral. She however continued restless till 6 A.M., when she fell into a sound sleep. During the night the temperature gradually fell, and at 8 A.M. Aug. 28th, it was only 100° Fahr.

On the 28th she complained of a return of her rheumatic pains in elbows and wrists. Till this time, since the first bath, she had been free from rheumatic pains. On examining her chest we heard loud double pericardial friction over the whole heart region, and detected pneumonia of both bases, but only posteriorly, the pneumonia being proved by dulness, tubular breathing, and crepitation. The temperature was recorded hourly, or every two hours, throughout the day. It remained below 100°·5 till noon, when it rose to 101°·2, but fell again at 9.30 to 101°·8, and steadily fell through the night, and on the following morning at 9 A.M. the thermometer recorded a temperature of 100°·5.

On Aug. 29th, throughout the day the temperature rose—at 5 o'clock reaching 102°·8 and at 9 o'clock 103°; but during the night it fell again, till at 3 A.M. it was 100°·8, but again rose.

On the 30th the upper line of heart dulness reached to the second rib, and loud pericardial friction was still audible. We also detected the great dulness of back, reaching to the angle of the scapula on the right side, but not quite so high on the left. There was distinct tubular breathing, but no rhonchus, nor expectoration, nor cough. Her respirations were 36 per minute. Subsequently her temperature rose daily to 102° Fahr. till Sept. 7th, and then gradually fell daily till the 11th, after which it became and continued natural. On Sept. 3rd we found considerable pericardial effusion, the dulness reaching to the clavicle, and the friction was much less distinct. There was very little evidence of pneumonia. The effusion diminished by Sept. 5th, the cardiac dulness only reaching the second rib. She

suffered from slight rheumatic pains in many of her joints till Sept. 15th. She was discharged Oct. 12th, cured.

It will be seen that this case confirms Dr. Fox's conclusions from his carefully recorded cases, that the temperature falls some time after removal from the bath. It also shows the marked effect of ice-bags, though it was probably greater in this case than many others, owing to the woman being small and spare. It also shows that pericarditis does not contra-indicate this treatment, and that when it increases the pericarditis and produces double pneumonia, yet the patient may recover. The pneumonia in this case was certainly peculiar, and appears to me allied rather to hypostatic than to ordinary lobar pneumonia. Thus the dulness ran along the back of the lung, leaving the anterior part but little affected. It excited no cough, produced no expectoration, hurried the breathing but very little, and did not heighten the temperature.

My experience of these cases leads me to conclude that the indications of approaching hyperpyrexia are delirium, high temperature, and disappearance of joint pain, though no doubt this combination not uncommonly occurs without an excessive elevation of the temperature, and, taken singly, each of these phenomena is of little value. For we meet with cases accompanied by high fever and very little pain, which nevertheless proceed satisfactorily. This is notably the case with children, in whom, as is well known, the joint affection is often extremely slight, whilst the fever is high. Again, the mere subsidence of the pain without a diminution of the fever does not threaten hyperpyrexia, as in many cases by mere rest the joint affection almost disappears, although the temperature may not abate. Again, we occasionally meet with cases at first puzzling, where there is persistent fever for days, even weeks, without joint and heart mischief, when perhaps pericarditis, soon followed by joint affection, declares the nature of the case. Neither does a high temperature predict an attack of hyperpyrexia, for these attacks not uncommonly occur in mild or only moderately severe cases. Indeed, as I have shown some years back, an attack of hyperpyrexia may occur without any of the indications mentioned, for a girl who recovered from rheumatic fever, and was to leave the hospital in a few hours, became suddenly

unconscious, and her temperature was found to be 110°, and continued as high till her death a few hours after.

Dr. Fox thinks suppression of perspiration is a serious symptom, and is a sign of impending danger. My experience, however, does not confirm this statement. The patient whose case has just been described, perspired freely before her attack. On the other hand, we meet with cases where sweating ceases without a decline of the other symptoms, and yet hyperpyrexia does not supervene. Again, it often happens that patients whose skin remains dry throughout the attack, progress favourably. This is notably the case with children, who, as a rule, perspire much less with rheumatic fever than adults. I beg, in conclusion, to draw attention to another circumstance, probably well known to most doctors, but not sufficiently dwelt on, namely, the influence of age on rheumatism. I am not referring to the fact that children generally have very little joint affection although the fever is high, nor to their greater liability to heart affection than adults, but to the influence of age on the duration of rheumatic fever. In children under ten years of age this disease seldom lasts longer than ten or twelve days, and often declines in six or eight, even when the patient is untreated; and we rarely if ever meet with chronic cases, such as occasionally occur in young adults, and which are common in middle-aged people, where the fever continues forty, fifty, sixty, or more days, the fever sometimes continuing high (103°) throughout, or is high at the commencement and then falls and remains between 100° and 101° for a considerable time, accompanied sometimes with severe, but often with very slight, joint pain, so that the patient gets up daily and is able to do a little work. In some cases we meet with a temperature which rises to 101° for a week or ten days, then becomes natural for a few days, and then rises again; these variations being repeated over and over again.

The treatment of this case was conducted by Messrs. Rigden, Curtis, and Taylor, to whose careful attention this woman undoubtedly owes her life.

A CASE OF RHEUMATIC FEVER TREATED WITH A COLD BATH; DEATH OCCURRING IMMEDIATELY ON LEAVING THE BATH.

BY SYDNEY RINGER, M.D.

THESE short notes are published as this case will help to answer the following questions:—Can cold baths be administered in rheumatic fever without danger? and is it advisable before employing this treatment to wait for the onset of hyperpyrexia? or should we commence it when high fever, absence of joint-pain, suppression of perspiration, and delirium show that there is danger that hyperpyrexia may occur? As hitherto all cases of rheumatic hyperpyrexia have proved fatal unless treated by cold baths, it is obvious that this case in no way contra-indicates that treatment on the occurrence of this dangerous condition.

A young woman, aged 24, was admitted into University College Hospital with rheumatic fever. Her father died suddenly from some unknown cause. Four years before the patient suffered from a severe attack of rheumatic fever. Her present illness begun about a week before her admission into hospital. On her admission she suffered from a sharp attack of rheumatic fever; her temperature rising daily to 103°. There was not, however, much joint affection, and at first she perspired freely, but latterly her skin grew dry. She rapidly got worse: thus during the nine days she was in hospital her temperature rose daily till it reached 105°, and her respirations rose from 32 to 60; her pulse remained about 120 per minute, and throughout was strong. Latterly she suffered from dyspnœa, and subsequently was propped up in bed with pillows. She wandered

a little at night, and on the day the bath was employed her intellect was a little obscured, and she passed her urine under her. At 7.42 P.M. of the ninth day of her admission she was placed in a general bath of 92°, her temperature in the axilla being 105° Fahr. In seven minutes, and before the temperature of the bath was reduced, her rectal temperature was 105°·8; the temperature of the bath was then reduced. In eighteen minutes after the commencement of the bath her rectal temperature was 105°·4. After forty-four minutes her temperature had fallen to 103°·4, the temperature of the bath being 69°. Whilst in the bath she took 4 ozs. of brandy. She was removed because her breathing grew rather shallow. After being put to bed she merely gasped a few times for five minutes and died, notwithstanding the employment of artificial respiration, energetic friction to the surface of the body, and anal injections of brandy. At the post-mortem examination we found a few patches of recent lymph on both lungs, but not an unnatural quantity of serosity in the pleuræ. The heart was universally adherent to the pericardium, the adhesions being tough; the blood in the heart and great vessels was very dark-coloured fluid and free from clots. The left ventricle and auricle were dilated—especially the auricle. On the tricuspid, mitral, and aortic valves, numerous minute vegetations were seen at the usual places. The mitral, aortic, and pulmonary valves were a good deal thickened. The mitral valves admitted three fingers nearly to the knuckles; the two segments were united for a short distance; they permitted some regurgitation when tested at the tap. The heart's substance looked healthy, and was of fair consistence. On the surface, at places, there was a thin line of paler and rather opaque tissue. The walls of the left ventricle at the base were $\frac{1}{2}$ inch thick, at the middle $\frac{5}{8}$ inch, and at the apex rather less than $\frac{1}{4}$ inch. The brain, liver, spleen, kidneys, stomach, and intestines were healthy. During life her urine contained a trace of albumen.

NOTES OF FIVE CASES OF PARACENTESIS THORACIS.

BY SYDNEY RINGER, M.D.

I AM induced to publish these few cases because they assist to answer some important questions concerning pleurisy with effusion and the operation of paracentesis thoracis. They show, what indeed is well known, how slight a disturbance this operation causes, and what immense relief it affords. They show that the operation may be usefully employed in the febrile and non-febrile period of the disease, and that during fever the fluid may be withdrawn by the aspirator, and not accumulate again. They prove, moreover, that in some cases of febrile and non-febrile empyema it is sufficient to withdraw part of the fluid by the aspirator, and that the rest of the pus may disappear; and that it is not always necessary to lay open the chest in order that the pus may drain entirely away. Moreover, they show that in severe empyema the temperature may be normal, or scarcely at all raised, and in those cases accompanied by chronic fever the pus may be perfectly sweet.

The following case of simple acute pleurisy of the left side occurred in a child twenty-five months old. On the tenth day of the disease, and when the fever was still high, the fluid had accumulated in such quantity that the heart beat a little inside the right nipple, and percussion dulness reached to the right edge of the sternum. The breathing was greatly oppressed, and the face and hands were livid. Indeed, it was obvious that tapping afforded the only hope of saving life. Mr. Durham, in the presence of Sir William Jenner, Mr. Clover, and myself, tapped the chest over the cardiac region, and withdrew with the

aspirator twenty-three ounces of clear serum. The child was at once relieved; the breathing became calm, the lividity disappeared; indeed, the improvement was so great that the friends asked if all danger was passed. However, as we expected, the fluid rapidly re-accumulated, so that in twenty-four hours the symptoms and physical signs were as bad as before the operation. Mr. Durham again tapped the chest (twelfth day of the disease), and withdrew with the aspirator seventeen ounces of rather turbid fluid, probably slightly purulent. The child was again greatly relieved, though less than after the first operation. He was, however, so exhausted that he died early next morning. The first operation caused scarcely any pain, but towards the end of the second the child became somewhat distressed.

The foregoing is a good example of one common form of acute pleurisy leading rapidly to effusion, and where the fever lasts usually only five to ten days. The following successful case belongs to another and common type of the acute disease with serous effusion, where the disease often sets in insidiously, and the fever lasts about twenty-eight to thirty days. It shows that even during the fever period the fluid may be withdrawn by the aspirator without any return of the effusion; nay, that the fluid left in the pleura may entirely disappear before the fever declines, and that in cases of this kind the operation may not affect the fever. Of course in these cases the patient is greatly relieved, and no doubt, if the operation is performed early, the lung is saved from great permanent disablement.

Anne Bannister was admitted into University College Hospital under my care on the 8th Sept., 1873. It was difficult to learn exactly the time the illness began. A month before admission she complained of pain in the right side and shortness of breath; in a fortnight a severe hacking cough set in. When admitted there was some lividity of the face, with fulness of the jugular veins on lying down. A physical examination showed that the right side contained a very considerable quantity of fluid. There was general bulging of the right side, with obliteration of the intercostal spaces. Percussion dulness reached across the sternum to a finger's breadth to the left of the sternum. There was very slight resonance in the right

interscapular region, and close to the spine in the infrascapular region. As is often the case, notwithstanding this extensive effusion, slight vocal fremitus was felt over the right back. Over the greater part of the diseased side, except at the base, both back and front, the breathing was very amphoric, and most perfect pectoriloquy was heard. The heart beat about two inches outside the left nipple. On Sept. 10, Mr. Crocker, the resident assistant in charge, made an exploratory puncture with a hypodermic syringe in the fifth interspace in the posterior part of the axillary region, and withdrew a small quantity of serum. The trocar of the aspirator was then inserted at the same spot, and fifty-six ounces of clear serum was withdrawn. As is usual, the withdrawal of the fluid and the expansion of the lung excited some cough, but less than generally occurs. The serum, when put aside, in a short time set into a solid jelly. A small portion, when boiled, coagulated and became solid. The position of the heart was not much altered by the operation, and though the resonance improved, much dulness remained, there being good resonance in front as low as the fourth rib, but the rest of the chest remained almost absolutely dull. Day by day the right side slowly retracted. On the 27th the retraction, both front and back, was considerable. There remained considerable relative dulness of the whole of the right side; this, as usual, being most marked in the axillary regions. The patient was sent to Eastbourne, and on Nov. 8 the physical signs were almost the same as before she left; thus the right shoulder was much depressed, the right side much retracted, especially behind. There was relative dulness over the whole right front, the dulness increasing as we descended the chest, and becoming absolute below the nipple. Respiration was very weak, blowing, and towards the base rather cavernous; the expiration was much prolonged. Expansion was very deficient. The percussion note was natural, behind, in the supra-spinous fossa and interscapular region; slight resonance below, close to the spine, but absolute dulness external to this and in the axillary regions. The respiration was very weak. The heart-sounds were very distinct over the right side, much more so than over the left. A slight cough remained, with slight shortness of breath on exertion. She was in excellent

health. In order to learn if the remaining dulness were due to serum, condensed lung, or lymph and thickened pleura, several exploratory punctures were made with a hypodermic syringe soon after the operation, but no fluid was withdrawn, except on the first occasion; hence we concluded that the serum left was absorbed. On the day of admission her temperature rose to 103°·6, and continued to rise daily to 103° and 104°·5 till the 16th (operation Sept. 10). On the evening of the operation it rose 0°·4 higher than on previous or subsequent days. On the 16th the temperature only reached 102°. It then gradually fell daily. On the 17th the maximum was 101°·6; on 18th, 100°·4; 19th, 100°; 20th, 101°; 21st, 100°·2; 22nd, 101°; 23rd, 100°·6; 24th, 100°·6; 25th, 99°6; and from this date, with the exception of an occasional slight elevation, it remained natural. The temperature was taken in the rectum six times daily, at 3 A.M., 7 A.M,, 11 A.M., 3 P.M., 7 P.M., and 11 P.M.

The next two patients suffered from right-sided empyema. In one case there was no fever; in the other the temperature rose to 99°·4, and occasionally to 100° Fahr. But 99°·4 is scarcely beyond the limits of health in a child. These cases show that there may be no fever in very extensive purulent pleurisy; and as both patients completely recovered after tapping with the aspirator, they prove, contrary to the opinion generally held, that it is not necessary in cases of empyema without fever to lay open the chest, nor to use a drainage-tube to permit the pus to drain completely away; but that the pus left after tapping with the aspirator may become rapidly absorbed. The pus in both these cases was quite sweet.

Arthur Shaw, aged two years, was admitted under my care Aug. 2, 1873. Three months before admission he began to lose flesh, his appetite became bad, and he passed blood and slime with his motions. He grew gradually worse, till seven weeks ago he was too ill to leave his bed for three weeks. At this time he first began to cough. He was taken to Brighton without benefit, his cough growing worse. On returning to town his mother took him to Mr. Langmore, who discovered pleurisy with extensive effusion, and sent him into the hospital. On admission we found the whole right side almost absolutely

dull, except in the interscapular region, and the dulness reached across to the left edge of the sternum. His heart was a little displaced, the maximum impulse being in the nipple line. On Aug. 4, Mr. Crocker, at my request, tapped the chest in the fourth interspace, just outside the right nipple, with the aspirator trocar, inserting it about two inches, but as only blood escaped it was withdrawn, and an exploratory puncture made with a hypodermic syringe in the fifth interspace in the axillary line, and some pus was withdrawn. The aspirator trocar was then inserted at the same spot, and fifteen ounces of sweet pus withdrawn without a bad symptom, the front of the chest becoming much more resonant. The breathing was much relieved. On Aug. 6 we noticed that the right side began to retract. As a good deal of dulness over the greater part of the right side remained, especially of the axillary region, we determined to tap a second time, and Mr. Crocker thrust the aspirator trocar through the sixth interspace (I think in the axillary region, but unfortunately on this point no note was taken), and withdrew six ounces and a half of sweet laudable pus. The operation excited no bad symptoms. From the first operation (and the second in all probability was unnecessary) the child was much more comfortable, and he greatly improved in appetite and strength. His side continued to retract, and on Sept. 3 the right side was decidedly smaller than the left. There was an excellent percussion note over the front of the right chest, in fact the note was hyper-resonant. There was great dulness of the whole back, and still more so of the right axillary regions.

On Sept. 5 the child was attacked with sore throat, which raised the temperature for a few days. On Sept. 24 the physical signs were much the same, but the dulness was a little less marked over the back, and, as usual in these cases, it was most marked in the right axillary regions, growing less on passing backwards to the spine, except at the extreme base, which continued equally dull to the spine. The spine was straight, and the heart in its natural position. In order to learn if the remaining dulness was due to fluid, several exploratory punctures were made at different times with a hypodermic syringe, without obtaining any fluid. These exploratory punctures

caused very little pain, and no subsequent trouble. The child was sent into the country, and returned in perfect health, the physical signs remaining the same.

On the day of his admission (Aug. 2) his temperature remained normal. Next day it rose to 100°, and on Aug. 4, the day of operation, it rose to 100°·4; and subsequently rose daily to 99°, sometimes to 99°·6, and in a few rare instances to 100°. As I have said, for a few days there was decided fever from sore throat.

Ellen Jane Moore, aged 4½, was admitted Sept. 1, 1873. In May she was seized with "inflammation of the lungs." She recovered slowly, but on Aug. 24 was again ill, and "had a return of her old complaint." On admission the child was rather emaciated, and exhibited a strongly-marked tubercular look. Her breathing was rather laboured. There were evidences of extensive effusion into the right pleura. The right side was enlarged and absolutely dull, with the exception of slight resonance in the interscapular region and close to the spine below. The dulness reached to a finger's breadth to the left of the sternum, and the respiration, as is often the case with children, was amphoric over the upper half of the right front and sternum. The heart's impulse could be seen and felt over a very extended area, reaching from the epigastrium to two fingers' and a half breadth outside the left nipple. On Sept. 4 we determined to perform paracentesis. An exploratory puncture was made in the fifth interspace in the axillary line with a hypodermic syringe, and some purulent fluid was withdrawn. The aspirator trocar was then inserted at the same spot by Mr. Crocker, and nineteen ounces of greenish yellow, sweet pus withdrawn. The operation caused very little pain, and no bad symptoms. After the operation the heart beat one inch outside the left nipple. All the child's chest troubles at once left her, and from this time she steadily improved, gaining flesh daily. A good deal of dulness remained after the operation. The chest slowly retracted. The breathing continued cavernous over the right front for some time. On Sept. 27 there was great dulness below the nipple, and much relative dulness over the back, the most resonance being situated in the interscapular region and close to the spine

below; the dulness, as usual, increasing as we passed outwards, and becoming excessive in the axillary regions and also at the extreme base, even close to the spine. The movements of the right side were much impaired. The heart beat in the nipple line. To ascertain if the remaining dulness was due to pus or serum, several exploratory punctures with a hypodermic syringe were made over the dull part of the chest, but without obtaining any fluid, and the child was sent to Eastbourne for a month, whence she returned in the most robust health.

The maximum temperature before the operation was 99°. On the evening of the operation and next day the temperature reached 99°·4; for the next eight days it only rose to 99°. Subsequently, on one or two occasions it rose to 100° Fahr. Like the former case, the child had an attack of fever, beginning on Sept. 12, and lasting four days, the temperature rising daily to 100° and 101° Fahr.

The temperature in these two cases was taken in the rectum six times daily, at 3 A.M., 7 A.M., 11 A.M., 3 P.M., 7 P.M., and 11 P.M.

The last patient, William Ringe, aged 47, was admitted under my care, Aug. 2, 1873, with right-sided empyema. There was daily fever, the temperature rising to 101°·5 and 102°·5, and sometimes to 103°. In addition, however, to the empyema, he expectorated pretty freely; and two days before paracentesis he spat a slight streak or two of blood. During the operation and for a few days after, the streaks of blood were much more numerous, indeed the sputa were deeply stained. This ceased, and he did not spit blood again. The expectoration, with this small quantity of blood, led us to think there might be phthisis as the cause of the empyema, but there were never any physical signs to lead to such a diagnosis, and moreover the expectoration grew much less, and the temperature became natural, and the patient wonderfully improved in health—in fact, looked and felt quite well. We felt bound, therefore, to conclude that probably there was no phthisis. If this opinion is correct, this case shows that febrile empyema of some standing may recover after tapping without laying open the chest or draining off the pus with a drainage tube. If the patient were phthisical, it shows that, with this grave complication, mere tapping with the aspirator may be sufficient to cure.

In this case the disease began acutely on July 15; previous to this he was in perfect health, with the exception of occasional attacks of gout. On that day he was seized with vomiting, back-ache and headache, and became light-headed. On the third day cough and diarrhœa set in, the diarrhœa continuing ever since, occurring directly after food. He had pain on the right side and at the pit of the stomach. The illness had considerably reduced his strength.

On admission, the chest movements on the right side were much impaired in front, except under the clavicle. Percussion note under the right clavicle was high pitched, and there was almost absolute dulness in the third interspace, and quite in the fourth. Vocal fremitus could be felt over the first and second interspaces, but not below. The left side was healthy; percussion note was rather hyper-resonant, and rhonchal fremitus could be felt over the whole left front and over the right apex. The heart's apex could not be felt. The right back scarcely moved at all, and was a little less prominent than left. Vocal fremitus could not be felt on the right side below the angle of the scapula. Percussion high pitched over upper part of right back, and absolutely dull below the angle of the scapula. Some sonorous rhonchus was heard at the left base. On a subsequent occasion a little mucous rhonchus was heard over the right back. The breath sounds were very weak over the lower half of the right side. On the 17th a puncture was made with the hypodermic syringe in the eighth interspace of the right side, in a line with the angle of the scapula, and a few minims of pus were withdrawn. Next day (18th) paracentesis was performed at the same spot with the large aspirator by Mr. Barlow, the resident officer in charge of the wards, and thirty-four ounces of pus were withdrawn, of the consistence of arrow-root, with numerous curdy flakes. The pus was quite sweet. The canula had to be cleared out several times, and once or twice withdrawn and cleared and reintroduced; and once it was inserted through the seventh interspace. The patient suffered a good deal of pain in the muscles of the side on moving; this, however, soon wore off, and he felt decidedly relieved by the operation, although the physical signs were scarcely altered, there being only a slight improvement in the percussion note of the right back. The vocal

fremitus was unaltered. Mucous rhonchus was heard in a few days over the whole of the right back.

On the 24th the signs were very little altered, the fever and expectoration continuing as before, but he expectorated with greater ease. On the 29th we noticed that there was increased retraction of the whole of right side, and the shoulder had sunk a little. There was scarcely any movement of the right side. Full vocal fremitus could be felt over the right base behind, and there was no absolute dulness below the angle of the scapula. The rhonchus had greatly decreased. The right side continued to retract. Vocal fremitus was distinctly felt over right base and axillary regions. Coarse rhonchus was heard over the left lung. His fever remained high for some time, and then declined and became natural ; his general condition at the same time wonderfully improving, and he was sent to Eastbourne quite convalescent. An exploratory puncture was made just before he left, over the dull part of his chest, with a hypodermic syringe, but no fluid could be detected in his chest.

This last patient appears to be a good instance of a not uncommon case, where there is a history of slow loss of flesh and strength for weeks. On examination dulness is detected at one base, with diminished or natural or even increased vocal fremitus. The lower part of the side is rather retracted, and respiration is very weak. There is considerable fever every night, rising to 101°, 102°, or 103° Fahr. The symptoms continue perhaps for several months, the retraction of the side slowly increasing, and then the fever gradually falls, at last becoming natural, when the patient improves in strength and gains in flesh. In these cases it is extremely difficult to know if the symptoms are solely due to empyema or are due to phthisis also (there may be a good deal of expectoration without phthisis) ; and unfortunately the temperature does not help us to decide.

A SUCCESSFUL CASE OF TRAUMATIC TETANUS TREATED BY LARGE DOSES OF CALABAR BEAN.

BY SYDNEY RINGER, M.D.,

Professor of Therapeutics at University College, and Physician to University College Hospital.

I AM induced to publish this case on account of the very large doses of Calabar bean that were administered, the irregular course of the symptoms, and the successful result.

On the evening of the 12th of September I received a letter from Dr. O'Leary, Professor of Materia Medica and Therapeutics and of Forensic Medicine at the University of Cork, then staying in London, saying that he feared he was attacked with traumatic tetanus, and requesting my prompt attendance. Dr. O'Leary told me he had been ill in bed three days; that six weeks previous he was thrown from his horse whilst riding a steeplechase at Punchtown, and inflicted a wound on his leg, which formed an obstinate ulcer, which he irritated a few days before his illness by pulling on riding breeches, to try a horse at Alexandra Palace Horse Show. There was an oval ulcer about two inches long and one-and-a-half broad, on the left leg, which Dr. O'Leary was dressing with "phenilonitric" acid. Whilst examining the leg several of its muscles became for a few seconds rigidly contracted, and then they became relaxed; then in a few seconds the muscle of the right thigh became affected, and even the muscles of both legs. Similar attacks occurred every few seconds, affecting sometimes only a few, at other times involving most of the muscles of the legs. The abdominal muscles were much more rarely and far less severely

affected, and those of the neck occasionally felt stiff. The upper extremities, chest and jaws, were unaffected. Dr. O'Leary protruded his tongue and swallowed readily, and without producing any tetanic contractions. The spasms were not brought on by external irritation, for they were not produced by irritating the limb, nor by that of getting out of bed. His pulse was feeble, and beat 120 per minute. The breathing was calm. I ordered him 30 grains of chloral and 10 of laudanum. Next morning, the fourth day of illness, I found him much worse. He had had no sleep. The spasms, now frequently recurring, involved his arms. During an attack the muscles of the legs, abdomen, and arms became powerfully contracted, and the abdominal muscles were as hard as boards. The tetanic seizures only remitted, for on the decline of each paroxysm, more or less rigidity still remained. He complained of slight stiffness of the neck, but the muscles of the chest and jaw remained unaffected. He looked very anxious. I immediately ordered him $\frac{1}{3}$ gr. of extract of physostigma every quarter of an hour by the mouth, and I may here say that throughout he took the medicine in this way. He commenced the medicine at 10 A.M., Sept. 13. His bowels were very freely open in the night. Sir James Paget kindly visited him with me, and was much struck by the irregular course of the disease.

At four in the afternoon, after taking about 5 grains of the extract, Dr. O'Leary was considerably better. The paroxysms were much less severe, and scarcely affected his arms, and between the attacks the leg muscles were quite flaccid; the attacks, in fact, had become intermittent instead of remittent. His expression was much less anxious, the skin moist and slightly perspiring, and his pulse beat 60.

At 10 P.M., having taken 10 grains of the extract in the twelve preceding hours, he was surprisingly better, the muscles being quite flaccid, and since last report he had undergone only one slight attack. He had taken plenty of food. His bowels were well open. P. 68, still small. He looked calm, and had slept about two hours, being roused every quarter of an hour for his medicine. The medicine had produced slight loss of power; his arms and legs, especially his legs, feeling rather heavy.

Sept. 14.—On this the second day of treatment, at 9 A.M., Sir James Paget again saw Dr. O'Leary with me. Last night he took 30 grains of chloral and 10 drops of laudanum, and $1\frac{1}{3}$ gr. of extract of Calabar bean every hour, making 20 grains of extract in nineteen hours. He slept well; has had no spasm since last report, so that with the exception of one slight attack he has been free from spasms for sixteen hours, and, indeed, he looks quite well, and feels neither sore nor bruised. There is no paralysis, not even a sensation of heaviness from the medicine. He was so well that we discontinued the drug.—8 P.M.: He has passed a capital day, having experienced only once or twice very slight attacks of rigidity of the hands, abdomen, and legs, on getting out of bed to pass water, and occasionally on moving his legs the muscles of the great toes became slightly tetanic. At bed-time he took 30 grains of chloral and 10 of laudanum.

Sept. 15.—At ten last night the paroxysms suddenly returned with terrible severity; the first attack producing complete opisthotonos, with jaws firmly fixed. The paroxysms occurred every few minutes, increasing in severity. They were so severe at 2 A.M. that the nurse several times thought he would have died from asphyxia. Unfortunately I was out of town, and could not see him till 10.30 A.M., and at this juncture Sir James Paget was obliged to leave town, so that I lost the advantage of his assistance. On the return of the paroxysms he recommenced the Calabar bean, $\frac{1}{3}$ gr. every quarter of an hour. When I saw my patient the medicine had produced no effect. His paroxysms were terrible. His jaws were firmly clenched. During each attack his body was first strongly bent backwards, only his head and heels touching the bed; and then in a short time he became bent forwards, so that the chin would almost touch his knees; then his body was bent from side to side, and as the attack passed off his arms and legs twitched violently, as if excited by powerful galvanic shocks. These frightful attacks, with slight remissions every few minutes, would last twenty minutes to half an hour. Sometimes the breathing was arrested by tetanic contraction of the respiratory muscles, till he grew blue-black in the face, and several times I thought he would have died from asphyxia. The sterno-mastoids and other muscles of his neck stood out

prominently. There was well-marked *risus sardonicus*, and he looked very anxious. Even when the paroxysm passed off, the extremities and muscles of the abdomen remained rigid, and he could not turn his head in the slightest degree to either side, nor bend it forward. Strange to say, external agents seemed to have very little effect in producing the attacks, for I examined him carefully, and handled his limbs without bringing on a convulsion. He swallowed slowly and with some difficulty, and after several mouthfuls a paroxysm came on. Talking did not excite the convulsions. At 10.30 A.M. I gave him $\frac{2}{3}$ of a grain of extract, and repeated this at 10.40 and 10.45, and then he took $\frac{2}{3}$ gr. every quarter of an hour. The attacks continued to be very severe, lasting, with slight remissions, from a quarter of an hour to twenty minutes, but the interval between them increased. The attacks occurred at the following times: 11, 11.9, 11.25, 11.45, and 12.25. He was in imminent danger of asphyxia, and on the decline of the paroxysm most of the muscles were in a state of tonic contraction. As it was evident that the medicine had not yet produced sufficient effect, at 12.45 I ordered $\bar{z}$ ss. of a mixture containing $\frac{1}{3}$ gr. to $\bar{z}$j, every quarter of an hour. At 2.45 a dose of the medicine was omitted, as symptoms of poisoning became manifest. At this time it was noted that the pupils were still only rather contracted. Pulse, 84; resp., 14; temp., 99°. Till this time the whole body had been persistently rigid, and he could not in the slightest degree move his head; but now, with the exception of his jaws being tightly clenched, his body is completely relaxed. There is slight general paralysis, he can raise his limbs slowly, but soon they slowly fall again. Moreover, he vomited a large quantity of fluid, and was able without assistance to raise and keep himself in the sitting posture. This movement did not bring on an attack. A slight seizure came on at 1.15, and another at 1.45; but, these excepted, he has been free since last report (two hours ago). Now, at 2.45, he took $\frac{1}{3}$ gr. of extract, and repeated it every quarter of an hour. A slight paroxysm took place at 3.20. At 4 P.M. the muscles had returned to their state of tonic contraction, and felt very hard, but he had undergone no fresh paroxysm; $\frac{2}{3}$ gr. of extract was ordered every quarter

of an hour. At 4.40 he had a severe paroxysm, lasting ten minutes, which arched him forwards; he then began a grain of extract every quarter of an hour. At 5.15 he experienced a slight attack, affecting only the muscles of the neck, with occasional spasms in both thighs. At this time there was very slight permanent rigidity of the trunk or extremities, but the jaws remained firmly clenched. The pupils were not extremely contracted, and his sight throughout has remained unaffected. He can now move his head a little from side to side. At 5.35 a slight paroxysm set in, lasting about a minute, and at 6.10 a very severe one lasting nineteen minutes. During the last twenty hours he has taken 40 grains of extract, of which 30 were taken within the last ten hours. At 8 P.M. he had a slight paroxysm limited to the muscles of the neck, but with this exception he has been free for an hour and fifty minutes. At this time he was quite quiet. For the first time since his relapse he could just separate his teeth. He could move his extremities, which seemed to him heavy. Pulse 80; temp. 100°. He vomited at 9.5, and had rather a strong convulsion at 9.53, lasting ten minutes. Since the vomiting he has fallen back, probably from rejecting some of the medicine which had not passed into his system. At 11 there was some persistent rigidity of his extremities, his jaws being again tightly clenched. His limbs felt heavy, but he could easily raise them. The pupils were strongly contracted. During the day he many times complained of severe colic and griping. At a little after 11 he took 40 grains of chloral and 20 drops of laudanum. He was ordered to take throughout the night 3 grains of extract every hour. At 12, midnight, he had a slight paroxysm, and then became restless and delirious, and got out of bed and walked about the room. During the day he stated that when he closed his eyes he saw faces and people walking about the room, these delusions disappearing directly he opened his eyes. At 1.15 A.M. he fell asleep. At 2 A.M. he had taken another 20 grains in the preceding eight hours. At 2.15 he had a severe paroxysm, lasting thirty minutes. At 3 he fell asleep, and slept soundly till 7.30.

Sept. 16.—At 8 A.M. Mr. Alfred Gould, who kindly joined me in attending Dr. O'Leary after his relapse, found our patient

sitting up in bed washing himself. His limbs were quite flaccid, but when moved they felt heavy ; slight trismus continued, but he could separate his jaws above half an inch. Pupils much contracted. Pulse 87, stronger ; temp. 97·6°. Ordered one grain of extract of Calabar bean every quarter of an hour. At 9.30 he finished another 20 grains of the extract, having taken this quantity during the preceding seven hours and a half. He got out of bed, stood unassisted, and then sat in a chair whilst his bed was made. I visited him at this time, and learned that he had had no attacks since the previous night. He lay quietly on his back, with his hands crossed. His muscles were all relaxed except those of the jaw. Colic and griping had entirely left him. He perspired a good deal in the night. He slept till 1, only roused at intervals to take his medicine. At 1, trismus had left him. All his muscles were relaxed, his limbs felt heavy, but there was no paralysis. Pulse 85 ; resp. 21 ; temp. 97°. Pupils strongly contracted. He complained of slight headache, and said that when he shut his eyes he saw pleasant visions, as persons presenting him with beautiful bouquets. He complained of a sensation of "haziness." When left alone he glided into an unobservant state, and would repeat over and over again part of a sentence, but on speaking to him he at once roused and finished it. He suffered from no nausea nor colic. Ordered to take $\frac{2}{3}$ of a grain of the extract every quarter of an hour. At 3.15 he became completely and even dangerously paralysed from the Calabar bean. The nurse, on offering him his medicine, noticed that his eyes trembled and his head twitched, and he appeared to struggle for breath and became very red in the face. This state continued for three-quarters of an hour, when the nurse, noticing that the false teeth had slipped, at once removed them, and the breathing became free. Dr. O'Leary's account of his condition at this time is that his jaw dropped, and he found that he had completely lost power over his muscles, that soon his diaphragm appeared to cease acting, and his breathing nearly stopped. He says his mind was quite clear throughout, but I think this could not be quite the case, as an hour and a half afterwards, at 4.45, when we saw him and when the paralysis had nearly passed away, we found his mind in rather a "hazy" state, and, as formerly, he repeated half a sentence

over and over again before he finished it. Still the functions of the mind could not have been much affected, as he gave a clear and graphic account of his state. Dr. O'Leary states that when most under the influence of the medicine, his sensations were very similar to those he felt when he took a large dose of hashish, some twenty-five years before, at a soirée at Alex. Dumas's, in company with Eugène Sue and other notabilities: he felt perfect repose of mind and body, with agreeable visions, which frequently changed, some assuming the form of angels and lovely women. This character of the visions Dr. O'Leary attributed to his having read shortly before one of Swedenborg's works. At 4.45 ordered to take $\frac{1}{3}$ gr. of extract three times in the hour. I need hardly say that the medicine was discontinued during the state of paralysis. At 6 P.M. he finished another 20 grains of the drug, having taken this quantity during the preceding eight hours and a half. At 7 P.M. we found him sitting up in bed, free from paralysis and spasm. He had had no attacks since those last reported, and had eaten some stewed eels. He said he felt quite comfortable, and had lost his "hazy feeling," and he did not repeat his words. His pupils were not quite so contracted; he perspired but little through the day. At 10 P.M. he expressed himself as feeling quite well, except that his muscles felt bruised. Ordered to take $1\frac{1}{3}$ grs. of extract every hour through the night. He took the medicine regularly till 4.15. At 4 A.M. he finished another 20 grains of the extract, when he fell asleep till 8.

Sept. 17 (9 A.M.)—He had been free from tetanic and paralytic symptoms. We found him sitting up in bed reading Greek. His limbs felt a little heavy. His pupils were less contracted. Pulse 87; temp. 98·4.° He said he felt quite well. To continue $\frac{2}{3}$ gr. of extract hourly. He remained quite well all day, and ate an ordinary dinner. In the evening his pulse was 87; temp. 100·8°.

Sept. 18 (9 A.M.)—During the night, not feeling sleepy, Dr. O'Leary sat reading and writing till 6 A.M. Still feels a little under the influence of the medicine. Temp. 99°. To take $\frac{1}{3}$ gr. hourly. At 12 noon he finished another 20 grains of the medicine. He got up for four or five hours and read. In the evening he said all feeling of heaviness and dimness of sight

had left him. His pupils were normal in size. Pulse 84; temp. 100·2°.

Sept. 19.—He continued his medicine through the night. He appeared quite well. We ordered him 1 gr. of his medicine every four hours. He dressed and went downstairs. On 20th he was so well that he came to the hospital, and was present whilst we made some experiments with the new Brazilian remedy, Jaborandi. He continued to take an occasional dose of his medicine.

This case is singular from the irregular course and from the rapidity of the disappearance of the symptoms. It is singular, too, from the fact that the spasms first attacked the lower extremities and gradually ascended the body. In the relapse, however, occurring on the discontinuance of the medicine, all irregularity disappeared, and the symptoms were those common to a very severe attack; the trismus, as usual, being the last evidence of the tetanus to disappear. The spasms were very little induced by external agents, even swallowing not readily bringing on an attack. Moreover, the attack yielded with unusual rapidity, for in thirty-nine hours after the relapse every vestige of the disease had disappeared. In treating this case we varied the dose of the medicine according to its effect; we attempted to keep up just sufficient paralysis to suppress the spasms. In spite, however, of very careful watching, serious general paralysis set in very suddenly, and that at a time when the patient was not taking the largest doses. However, these serious symptoms passed off in a short time. In respect to the dose of the bean, this case is less valuable than it ought to have been, on account of a dispensing error. The first bottle contained 10 grains of the alcoholic extract. Unfortunately the watery extract was subsequently dispensed by mistake. Still the results fully show that even this is a highly active preparation. In eighty-six hours Dr. O'Leary took 140 grains of the extract of Calabar bean; and of this, 88 grains were taken in thirty-two hours, that is, $2\frac{3}{4}$ grains per hour. For a short time he took 4 grains an hour. Even this large dose, however, has been exceeded, for Dr. Eben Watson reports a case in which 1,026 grains of the alcoholic extract were given in forty-three days. He gave small doses on the first day, but rapidly in-

creased the quantity, so that in a few days his patient took daily 16 grains, then 48 grains, then 57, and on one day 72 grains, without any serious amount of paralysis. We gave the medicine in moderate doses, repeating them frequently, so that on the advent of any serious degree of paralysis the further action of the medicine could be arrested; yet, spite of this precaution, probably from some inequality in the rapidity of absorption, serious symptoms did arise.

Various questions suggest themselves in connection with this singular case. Sir James Paget suggested that possibly the "nitrophenilic acid" Dr. O'Leary applied to his sore might have caused the symptoms, but I think this cannot have been the case, for the same applications had been applied on a former occasion for several days, without any tetanic symptoms; and further, Mr. Gould injected several drops under the skin of a cat without producing any symptoms whatever.

Did the Calabar bean cure the patient? I believe so; for on discontinuing it the symptoms recurred, but were again speedily suppressed by a return to the medicine. The recovery was certainly not due to the chloral and opium draught he took at bedtime, for the relapse occurred in spite of this draught.

Next in regard to the dose of the medicine administered. It may be said the extract was bad, but it was obtained of Mr. Morson, and was made in his laboratory. The large dose produced at first colic and sickness, but these symptoms speedily wore off. At first there was copious perspiration, but this I think was more due to the paroxysms than the medicine, for as soon as the spasms were subdued the perspiration almost ceased. There was no salivation. Moreover, the pupils were only slowly contracted, and did not become very small till the drug had been given for some time in very large doses, and after evident signs of partial paralysis had set in. Dr. Eben Watson noticed the same fact in his case. The sight also was very little affected. The brain was slightly affected, as is evident from the details of the case. During this severe and painful and dangerous illness, it was impossible not to admire the extraordinary coolness and courage and patience manifested by Dr. O'Leary. After the cessation of a severe convulsion which shook every fibre of his body, he would look at

us and smile, and say cheerfully, "Well, that attack is over." Mr. Gould and I felt it needful to visit him very frequently, and our patient, well aware of his danger, would say to us, "Oh, I give you too much trouble—you needn't come so often; I'm a cool hand, and I can watch the action of the medicine."

THE EFFECTS OF PILOCARPINE (THE ALKALOID OF JABORANDI) ON TWO CASES OF UNILATERAL SWEATING.

BY SYDNEY RINGER, M.D.,
Professor of Therapeutics at University College; and

J. S. BURY,
Physician's Assistant at University College Hospital.

[*Reprinted from* THE PRACTITIONER *for* DECEMBER 1876.]

A MAN and a woman, the subjects of unilateral sweating, were admitted into University College Hospital, and on testing upon them the effect of pilocarpine we obtained very curious and unexpected results. The first injection caused in both cases far more copious perspiration of the normal than of the perspiring side. The woman, on any exertion, perspired profusely over the whole left side. We subjected her to six experiments. On the first, the perspiration was much more abundant over the right side; on the next three occasions she sweated most on the left side; on the fifth most on the right side; and on the last, most on the left.

The man, admitted whilst apoplectic, perspired profusely without intermission over the right half of the head and face, and very freely over the right half of the chest and the right arm. We made five experiments on him. On the first occasion the pilocarpine caused free perspiration on both sides of the body, though far more profuse on the left than on the right side; on the four following occasions, the perspiration was equal on both sides of the face, but far more abundant over the left half than over the right half of his bald head. It is curious that the right half of the moustache did not grow till after the use of pilocarpine.

These injections produced another strange and unexpected

effect. The pilocarpine cured the woman, who had suffered for years from this unilateral sweating. The first injection much reduced the left-side perspiration, and the subsequent injections removed it altogether, and though she remained under observation for several weeks longer, the sweating did not recur. The effect of the drug on the man's perspiration was less marked, though the first injection very greatly lessened it, so that it only amounted to slight moisture, whilst previous to the use of pilocarpine the right side of the face and head was always covered with large beads of perspiration, which, running together, trickled night and day down his head and face, and most freely whilst he slept. After twelve days, however, in spite of repeated injections, the unilateral sweating returned, and thenceforward the pilocarpine utterly failed to control the sweating, for though it still induced copious perspiration, it did not, as formerly, afterwards lessen the abnormal amount of it. We then injected $\frac{1}{100}$ of a grain of atropia, which in ten minutes dried the sodden skin, and it remained dry, or only perspired very slightly on rare occasions, during the subsequent eleven days, when we discontinued our observations.

The woman had previously suffered from difficulty in holding her water, which the pilocarpine increased, so that for a short time she suffered from incontinence.

Our mode of proceeding was as follows:—We wiped the face quite dry and then gave the pilocarpine, and subsequently about every three minutes we wiped the face, and noted how soon the perspiration reappeared and in what amount.

Sarah Morris, æt. 46, admitted with paraplegia, which began ten years ago, and has continued slowly to increase. Nine years ago, she awoke one morning with the left side of her face and body bathed in perspiration, and since that time the unilateral sweating has persisted. About this period she noticed that her left side was the weaker, and that her left leg dragged more than the right. The hemiplegoid condition has now quite disappeared, the paraplegia remaining. At the present time, slight exertion, warm weather, a meal, or sleep, brings on a copious perspiration of the whole left side of the body, so abundant that at night her pillow and the left sleeve of her night-dress is soaked with sweat.

On August 10th we injected under the skin of the left arm $\frac{1}{3}$ gr. of pilocarpine, which brought on flushing of both sides of the face, especially of the right side, which to the patient at first felt hotter, and very soon she felt hot all over.

Perspiration appeared in seventeen minutes, at first equal on both sides, but three minutes later it was much more abundant on the right side, the difference being most marked, for while the left side of the face, arm, leg, and foot, were nearly dry, the corresponding parts of the right side were wet with perspiration. In twenty-five minutes the perspiration began to decline, though it was still far more abundant on the right side. We noted at this time that soon after wiping the face the left side was cool and dry, while the right side was hot and moist. The following night the left-side perspiration was very slight, far less than on previous nights. On the following day, August 11th, we repeated the experiment, injecting the pilocarpine into the right arm. Both sides of the face became equally flushed, but to the patient the right felt the hotter. On this occasion the perspiration was much greater on the left side of the face, the hands being equally moist. The left side of the face felt to the hand much colder than the right. On the 12th we repeated the experiment, injecting $\frac{1}{3}$ gr. of pilocarpine under the skin of the right arm. Both sides of the face became equally flushed, the sweating at first being much more marked on the left side of the face, the difference being most evident on the forehead. The hands were equally moist. Five minutes after, the perspiration became marked; we wiped the face, and after this, both sides of the face sweated equally.

On August 13th we injected $\frac{1}{2}$ gr. of pilocarpine under the skin of the left arm, noting previously that the left forehead was moist, the right dry. Both sides of the face became equally flushed. The left side of the body sweated much more than the right. We then injected $\frac{1}{100}$ gr. of atropia under the skin of the right arm. In five minutes the left side still perspired freely; in fifteen minutes the sweating had entirely ceased.

On August 18th we injected $\frac{1}{3}$ gr. of pilocarpine into the right arm, and the right side of the face and the right arm perspired more than the corresponding parts of the left side.

On September 6th we injected $\frac{1}{2}$ grain of the alkaloid into

the left arm. She perspired on the left side, but, strange to say, this large dose caused no perspiration on the right side, and not excessive sweating on the left side. It lasted only thirteen minutes. As we have already stated, the pilocarpine quite cured this woman of unilateral sweating.

In order to ascertain if the unilateral sweating was due to some affection of the vaso-motor nerves inducing an increased supply of blood to the sweat-glands on the left half of the body, we on four occasions administered nitrite of amyl by inhalation in sufficient dose to flush the face strongly. On each occasion the face flushed equally on both sides, and in one instance only did the inhalation cause slight perspiration, and this was equal on both sides of the face; the left cheek, the left temple, and left half of forehead, felt, during the flush, much cooler than the opposite parts, whilst the patient averred that the left side felt to her hotter than the right.

Joseph Liney, æt. 55, a cabman, whilst plying for hire on September 14th, 1876, was seized with right hemiplegia, and a few hours after the seizure he drove himself to the hospital, and was at once admitted. There was no loss of consciousness. There was almost complete loss of sensation of the right half of the trunk and right limbs, and only a little sensibility of the right side of the face. We tested sensation by thrusting a pin into the skin. There was slight loss of power in the right leg and great loss in right arm. There was slight loss of power of the right side of the face. The right pupil was generally larger than the left, and the sight of the right eye was a little weaker than the left, and there was right hemiopia. The hearing was a little affected on the right side. The tongue deviated to the right. The first, fourth, sixth, ninth, tenth, and eleventh nerves were unaffected. Apparently, nutrition was affected on the right side, for the right moustache did not grow, whilst the left grew naturally. Immediately after his attack he began to perspire profusely over the right side of the body. The perspiration was most marked over the right half of the face and neck and right half of his bald head. The perspiration always stands in large drops on these parts, and, as in the other case, is most abundant during sleep. There was no affection of speech and no emotional disturbance. He slowly mended; power, as usual, returning

soonest in the paralysed leg; but all the foregoing symptoms were well-marked when these experiments were made.

September 22nd, whilst the right side was bathed with sweat and the right pupil was larger than the left, we injected under the skin $\frac{1}{3}$ gr. of pilocarpine, which much increased the perspiration, at first most abundant on the right side. Ten minutes after the jaborandi began to act—the left side was perspiring most, and for thirty minutes continued to perspire much more than the right, when the sweating declined, becoming equal on both sides.

Six minutes after the injection the pupils were equal; in twenty minutes the right pupil was smaller, and so continued thirty-six minutes after the injection, when the pupils became equal. Forty-eight minutes after the injection, perspiration ceased. In the evening we found both sides of his face quite dry, though since his illness this had never been the case.

Next morning, September 23rd, we learned that there had been very little perspiration of the right side during the night, though previous to the use of the pilocarpine the perspiration had been more profuse during sleep.

At midday we found the right side of the face slightly moist, and a little moister than the left, and the right pupil rather the larger. We then injected under the skin $\frac{1}{3}$ gr. of pilocarpine. For a few minutes the perspiration was in excess on the right side; in eleven minutes the perspiration was equal on both sides; in sixteen minutes the perspiration was much more profuse over the left half of the head, but equal on both sides of the face, and so continued. In forty-four minutes the perspiration began to decline; in seventy-four minutes it ceased. In sixteen minutes the pupils were equal; in twenty-eight minutes the left pupil was a trifle larger than the right. On this occasion the pilocarpine caused very profuse perspiration.

All next day the perspiration was very slight, and could be detected only over the right parietal bone and the right side of the nose.

On September 25th we injected $\frac{1}{3}$ gr. of pilocarpine into the left arm, the pupils being at this time equal; in four minutes sweating had begun on the right side of the face, and in five minutes large drops of perspiration stood on the right side, with only a little moisture on the left. After this, the perspi-

ration became equal on both sides except on the head, being much greater over the left than the right half. In ten minutes the right pupil became larger than the left, but in thirty minutes the pupils became equal again. During the next eight days he was carefully watched, and the perspiration was found to be very slight, and generally there was no excess on the right side, but on some occasions there was slight moisture on the right, whilst the left side of the face was dry.

The right moustache meanwhile had begun to grow, whilst before there was no growth.

On October 3rd we repeated the injection, with exactly the same result, as regards sweating, as on September 25th. Before the injection, the left pupil was a very little the larger, and so continued throughout the experiment. On October 5th the perspiration of the right side became as profuse as ever, and on October 6th we injected another $\frac{1}{3}$ gr. of pilocarpine, whilst the right half of the head and face was bathed in perspiration. In eight minutes the perspiration was equal on the two sides, with no increase on the right, this side before the injection perspiring apparently as actively as the sweat-glands were capable of. The perspiration continued about equal on the two sides, but with a slight excess on the left side of the head. In thirty-five minutes perspiration ceased, but the same evening and next day the right-sided perspiration became as abundant as ever. As pilocarpine in this case had apparently lost its effect, on October 7th we injected $\frac{1}{100}$ gr. of atropia while the right half of his head and face was covered with beads of perspiration, and watched the result without wiping away the sweat. In ten minutes the perspiration had evaporated, leaving both sides of the head and face quite dry. We carefully watched the patient, and found that the perspiration of the right side was almost completely controlled till October 18th, at which date we discontinued taking notes.

A CASE OF ACUTE MANIA TREATED WITH LARGE DOSES OF HYOSCYAMIA, DATURINE, ATROPIA, AND ETHYL-ATROPIA.

BY SYDNEY RINGER, M.D.,

Professor of Therapeutics at University College; and

J. S. BURY,

Physician's Assistant at University College Hospital.

[*Reprinted from* THE PRACTITIONER *for* MARCH 1877.]

DR. ROBERT LAWSON, of the Wakefield Lunatic Asylum, in a valuable paper published in the *Practitioner*, recommends the employment of large doses of hyoscyamia in various forms of insanity. A case of acute mania being admitted under our care, and after large doses of opium had failed to produce sleep, we determined to try this drug. We also compared the effects of hyoscyamia with those of atropia, daturine, and ethyl-atropia, the latter a new preparation, prepared for Mr. William Murrell and ourselves by Mr. Wright, under the direction of Dr. Graham, Assistant Professor of Chemistry at University College.

We used sulphate of atropia; the crystalline hyoscyamia, prepared in Germany, and the daturine were dissolved with the assistance of sulphuric acid. Ethyl atropia, being soluble in water, was used without the addition of an acid.

The results in this case fully conform the strong recommendation of Dr. Robert Lawson, and they prove that atropia and daturine, if not equal, are of nearly equal value to hyoscyamia.

Eliza Reynolds, aged twenty-two, a nurse at University College Hospital, was noticed one night when on duty to be odd in her manner; next day she was unmistakably mad. She lay in bed with her eyes closed, disregardful of everything around her. She talked incoherently, and when asked a question made allu-

sion to a different subject. Her temperature was 99, pulse 104, her breathing irregular. Her bowels were constipated. Beyond her madness we could not discover any disease. Her manner soon changed, for next day she sat up in bed, looking vacantly around her, and continued in this state day and night, getting no sleep in spite of narcotics. Her delusion took a religious form, and she showed a suicidal tendency. She very rapidly lost flesh, her eyes became sunken, and this in spite of her taking a fair amount of milk and beef-tea. Her tongue was always dry, and her temperature normal. She passed everything under her. We felt unless we could give her sleep that she must soon die, and, as morphia had failed, we determined to use hyoscyamia. On the evening of October 25 we gave her a grain of the crystallised alkaloid, with most complete success. We then resolved to give atropia, and see if that would answer as well. We were afraid to give a grain of atropia, so on the first night we gave only a quarter of a grain, but without producing any sleep. We next gave three-quarters of a grain, and then a grain, and afterwards we employed daturine and ethyl-atropia. The effects of these different remedies are given subsequently in a table. With sleep the bodily health of the patient greatly improved, but her mind continued in the same feeble state.

The first dose of hyoscyamia flushed her face and hands a deep red, but this effect was not noticed afterwards. Her tongue, as we have said, was always dry before the use of hyoscyamia, and the day after the first dose it was still more so; but subsequently, to our astonishment, the tongue was always moist in the day time, though it became very dry for some hours after each dose of the alkaloid. We were astonished also to find that after the second or third day the skin was always moist during the day; during the early part of this treatment her tongue was very red, though moist and clean, but afterwards it became quite natural. About a week before she left hospital to go home she was allowed to get up, and she constantly walked slowly about the ward, kneeling down before the other patients. We were unable to take the pulse very frequently, or otherwise very closely study the effects of this large dose of hyoscyamia, as we were afraid lest we should wake her, and we felt that her life depended on her getting sound refreshing sleep. After the first

dose of hyoscyamia, the pulse rose from 104 to 144 in half-an-hour; in an hour it had fallen to 120, and then gradually declined, so that after eight or nine hours it was 100 again. The respirations were not hurried. After the second doses the pulse rose from 104 to 125. On the following nights the pulse was very little affected. On the twelfth day of her illness her pulse fell to 80. We may add that throughout her pupils were widely dilated. We now give a table showing the effect of the different alkaloids in producing sleep.

Date.	Medicine.	Time given.	Interval before sleep.	Duration of sleep.
1876				
Oct. 21	Liq. Morph. ♏xx.	Bedtime	—	None
,, 22	Same	,,	—	None
,, 23	Same	,,	—	None
,, 24	Liq. Morph. ♏ 100 (in three doses)	,,	—	None
,, 25	Hyoscyamia, gr. 1 (?)	4 P.M.	1 hr.	15½ hrs.
,, 26	Hyoscyamia, gr. 1	7 ,,	1¼ hr.	11½ hrs.
,, 27	Same	7·45 ,,	1¼ hr.	9½ hrs.
,, 28	Same	8·15 ,,	1¼ hr.	8 hrs.
,, 29	Sulphate of atropia, gr. ¼	5 ,,	—	No sleep
,, 30	Hyoscyamia, gr. 1	11·45 A.M.	1½ hrs.	11¼ hrs.
,, 31	Sulphate of atropia, gr. ¾	9·7 P.M.	1 hr. 8 m.	7¼ hrs.
Nov. 1	Sulphate of atropia, gr. 1	8 ,,	2 hrs.	7½ hrs.
,, 2	Hyoscyamia, gr. 1	8·15 ,,	1¼ hr.	9½ hrs.
,, 3	Daturine, gr. 1	8·15 ,,	1 hr.	8 hrs.
,, 4	Ethyl atropia, gr. 1	8·30 ,,	—	No sleep
,, 5	Hyoscyamia, gr. 1	10·15 A.M.	1 hr. 5m.	13½ hrs.
,, 6	Same	8 P.M.	1½ hr.	9½ hrs.
,, 7	Daturine, gr. 1	8 ,,	2½ hr.	7 hrs.
,, 8	Sulphate of atropia, gr. 1	8·15 ,,	2 hrs.	7 hrs.
,, 9	Hyoscyamia, gr. 1	8·30 ,,	2 hrt.	8 hrs.
,, 10	Daturine, gr. 1	8·30 ,,	2 hrs.	6 hrs.
,, 11	Sulphate of atropia, gr. 1	8·30 ,,	1¾ hrs.	6¼ hrs.
,, 12	Hyoscyamia, gr. 1	8 ,,	¾ hr.	7¼ hrs.
,, 13	Daturine, gr. 1	8·30 ,,	1 hr.	7 hrs.
,, 14	Sulphate of atropia, gr 1	8·30 ,,	1 hr.	7 hrs.
,, 15	Ethyl atropia, gr. 1	—	No sleep	—
,, 16	Sulphate of atropia, gr. 1	8·30 P.M.	1½ hr.	8 hrs.

Hence, excluding the first two nights with hyoscyamia, during which time the patient appeared to grow somewhat accustomed to the drug, and thus it seemed to lose some of its effect, we find that hyoscyamia on an average produced 9½, sulphate of atropia 7¼, and daturine 7¼ hours' sleep.

It thus appears that in cases of madness or delirium, sulphate of atropia and daturine are as good, or nearly as good, as the far

more expensive alkaloid hyoscyamia. Perhaps it may be objected that the sleep she latterly obtained was natural sleep, and not at all due to the alkaloids, but this cannot be true, for it will be seen in the preceding table that on the nights she took a too small dose of sulphate of atropia and on the night she took ethyl-atropia, she had not even five minutes' sleep; the nights were absolutely sleepless; we therefore conclude that the alkaloids did produce the sleep. The sleep was very heavy, but the patient could be awaked, but immediately relapsed into sleep again. Sometimes the breathing was a little stertorous. She slept with her mouth wide open. We have deferred publishing this case for some weeks, that we might learn how the patient progressed after leaving the hospital, as we felt that possibly the alkaloids might cause some of her delirium. We thought that this was improbable, for the delirium of belladonna usually subsides in less than twenty-four hours, and yet in this case, when ethyl-atropia (a drug which does not affect the brain) was given, and she had no sleep, the delirium was always worse the day following the sleepless night.

About a week after reaching home she began to improve, and in a letter, dated December 7, it says "for the last ten or eleven days she has been quite sensible. She is quite cheerful, but her eyes are too weak to read much at present." So we conclude that the effect of the alkaloids on her eyes had not quite disappeared twenty-one days after the last dose of alkaloid.

NOTES ON A CASE OF ATHETOSIS, PRECEDED BY HEMIPLEGIA AND HEMIANÆSTHESIA, AND ACCOMPANIED BY UNILATERAL SWEATING.

BY SYDNEY RINGER, M.D.,

Professor of Therapeutics at University College.

[*Reprinted from* THE PRACTITIONER *for* AUGUST 1877.]

JAMES SAMSON, bricklayer, aged 32, admitted into University College Hospital, January 15, 1877. Has been married thirteen years, and has four children. Always had sufficient food and clothing, and has never drunk to excess. He lived in London till 1869, since then in Canada. His father, aged 52, is subject to "dropsy in the leg." His mother, 53, is healthy; he has one brother who is healthy.

Present Illness.—On May 13, 1873, he drank more beer than usual, but was not intoxicated. He slept well during the night, but in the morning awoke with severe headache; but he got up and went for a walk, when a "dazzling came before his eyes," his sight became dim, he heard noises in his ears, and his face sweated profusely. He continued his walk, but feeling giddy, he looked for a seat, but not seeing one, walked on for a quarter of a mile, when he noticed that his "feet were crossing one another," and after about eight more steps he fell down on his right side and lost consciousness, he thinks only for a few minutes. When held up, on coming to, he suddenly felt as if a weight were falling off his head down the right side of his body to the foot. Taken to a seat and left for a short time, he fell off the chair, again on his right side, and could not get up. On recovering consciousness he found himself speechless, with loss of power and sensation in the right side and in the three

inner fingers of the left hand. His face felt "drawn to the right side." After a few hours he was taken to a hospital, where hot water was applied to his feet. He got up on May 24th, and left the hospital, after a stay of ten weeks. In the first week speech returned.

Sensation.—He quite lost sensation in the right limbs from May 13th to 22nd, being unable to feel even a needle thrust into the right arm or leg. In about ten days he felt "needles and pins" in his right limbs, and at this time sensation began to return. The upper limb felt numb for about a month, the lower for twelve months, the numbness lasting longest in the calf and outer side of thigh.

Motion.—He first became able to move his right limbs on May 22nd, power returning soonest in the arm. On May 24, "something seemed to rush down from the shoulder to the hand;" the arm seemed dragged down, and he felt "as if half a hundredweight were tied round his wrist." The hand became much swollen, and looked like "mottled soap." Every morning on getting up the same "rush" occurred, followed by swelling of the hand; at night the swelling had all gone. This rushing sensation from the shoulder to the hand lasted seven or eight weeks; it then stopped from that time to the present. His fingers "have gone all shapes," his arm, too, "used to go quick on his hand." The spasmodic incoordinated movement has gradually improved.

Memory.—Some weeks after the fit he forgot, when talking, what he had said, or what he wanted to say.

Headache.—Since the fit he has had darting pains in the right side of the head, which began about an inch above the right eyebrow, and passed through the head to the right half of the occipital region. There are always two darts of pain, and it is always worse in winter.

In the summer following the attack, on taking a warm bath, he noticed that he felt much warmer on the right side, and that the right arm and leg perspired much more than the left. This unilateral sweating has continued since, especially in summer, and even in winter, when he "feels very nervous." We have several times verified this statement.

The paralysis of the fingers of the left hand varied much,

getting better, then relapsing for about three years, and then steadily improving. He came to England last December.

Present Condition.—Patient is a small, somewhat muscular man: height 5ft. 3in. Hair black, turning grey. Face pale. Eyes greyish blue: arcus senilis just appearing: sclerotic injected and slightly yellow. Skin normal, no eruption. No sweatings. Temp. normal. He has an obstructive and regurgitant mitral murmur with a distinct presystolic thrill. The heart is neither dilated nor hypertrophied, but on exertion he suffers from palpitation. He has never had rheumatism.

Cranial nerves. — 1st—natural; 2nd—sight good, equal on each side, no hemiopia; 3rd—pupils contract a little to light, but perhaps not with normal readiness; no paralysis of the muscles of the eye; 4th—normal; 5th—normal; 6th—slight internal squint of right eye; 7th—slight deficient action of muscles of the right angle of the mouth; the right eyebrow is not raised so well as the left; 8th—normal; 9th, 10th, 11th, 12th—normal. Sometimes, when excited, the eye-balls "twitch."

The right upper and lower limbs are in a state of continuous spasm, chiefly noticeable in the hand and foot. The same muscles are not always affected; nor is there always the same degree of contraction, so that the spasm varies both as regards degree and the muscles involved. Voluntary power remains, but it is imperfect, but only on account of the "mobile spasm." Thus the performance of a trifling voluntary act often occupies some time, perhaps a minute, and is then usually an exaggeration and, I might say, a burlesque of the act aimed at. To make myself better understood, let me describe certain voluntary acts. When told to open his left hand, generally spasmodically closed, it is obvious that he is making a strenuous effort, and after a few seconds, or longer, the fingers slowly unbend, and become over extended, being separated widely apart, with the last phalanges curved backwards. Often the limb moves readily; thus in buttoning the left wristband, the right hand goes directly to the place and the fingers begin to act, but in a clumsy fashion. The button is seized by the thumb and forefinger, but they are pressed too tightly together to allow the button to glide into the button-hole readily, and the fruitless attempt increases the spasm. This exaggeration always occurred in voluntary move-

ment, till at last the spasm became strong enough to overcome voluntary movement, and the limb assumed an incoherent position. In voluntarily overcoming the spasm the first movement was his chief obstacle; thus, having with difficulty begun to open the hand, the farther extension was much more readily performed. The greater the existing spasm, the longer the time before the commencement of the initial voluntary movement, and the slower its performance. Sensation is equally good on both sides of the body.

The leg is quite as erratic as the arm, and the disease chiefly falls on the ulnar nerve and the branches of the sacral plexus, though all the branches of the brachial plexus, except those supplying some neck muscles, are affected, and some of the branches of the lumbar plexus are also involved. Some of the ulnar muscles were always affected, and I never saw any movement through other nerves without strong contraction of some, generally of most of the ulnar muscles.

When awake his right fingers and thumb are always flexed, though the position of the fingers and thumb varies somewhat. Told to open his hand, he does so slowly, and in the inverse order in which the fingers so frequently recontract; that is, the finger last to contract is the easiest to open. When the hand is opened, the fingers are widely extended, and the last phalanges a little bent backwards, obviously from strong action of the dorsal interossei muscles. Then in a short time, especially if his attention is diverted by conversation, voluntary extension becomes relaxed, the fingers become slowly flexed, first at the metacarpo-phalangeal articulation, so that the fingers are flexed straight, and are at the same time approximated, this combined movement being due to the palmar interossei. The little finger is the first flexed, and has nearly touched the palm before the ring finger begins to move, then follows the second, and last the forefinger. Next, the fingers become slightly bent at the first phalangeal articulation (superficial flexor), and at last the fingers are pressed firmly against the palm, the last phalanges still remaining flaccid, the deep flexor muscle not contracting. When the hand is closed the thumb becomes flexed and adducted into the knuckles of the fingers (ulnar nerve). This order of contraction is sometimes

departed from; thus, after the little and ring fingers have become partially flexed, the thumb is flexed and adducted into the palm, and the middle and forefinger become flexed over the thumb, its tip protruding between the middle and ring finger. Sometimes lesser degrees of the same movement occurred; thus the fingers were only partially flexed at the metacarpo-phalangeal articulation; or the ring and little finger were closed, whilst the middle finger was only slightly flexed, the forefinger being extended, or both ring and forefinger were extended, but the thumb was always in these different combinations more or less flexed and adducted.

In addition to these contractions others were often added of a very varying kind, giving a great variety in the combinations of different muscles, and in the degree of their contraction. Thus the wrist was often strongly flexed, mainly from contraction of the flexor ulnaris, but also in varying degree from the other flexor muscles. When due chiefly or entirely to the flexor ulnaris the hand was of course strongly adducted as well as flexed, the forearm was often very powerfully pronated from contraction of both pronators, and often in addition to strong flexing of the fingers and wrist the arm was bent on the shoulder from strong contraction of the biceps. Besides all these contractions, sometimes the arm was slightly raised by partial contraction of the deltoid, and the whole arm pulled a little back, the strongly pronated and contracted hand being brought close to the axilla.

At other times the forearm was strongly extended and drawn backwards behind the back, being sometimes turned inwards, at other times outwards, the extension being due to contraction of the triceps and the back position with rotation outwards to the deltoid, teres major, and infra spirales; the rotation inwards to the latissimus dorsi, &c.

Occasionally the forearm was powerfully supinated; and sometimes the extensor muscles were hard and rigidly contracted, but this occurred when the flexors were in the same condition, so that in no instance did we see the hand or fingers moved by the extensor muscles; these muscles contracting simultaneously only with many others, and especially the flexors. In fact, the musculo-spiral nerve muscles were

the least often affected, especially those supplied by the posterior interosseous nerve. The triceps and supinator longus were more often affected than the extensors of the hand.

Sometimes, from excitement, or when startled, the fore or middle finger, or both, being flexed at the time, would start out and become rigidly extended; but this extension was due to the dorsal interossei muscles, judging from the character of the extension, the first phalanx being rather flexed and the two last being bent rather backwards. Sometimes the shoulder was depressed, and was generally so when the arm was carried behind the back, this depression being due probably to contraction of the rhomboidei muscles. In no instance did we detect any movement of the neck muscles supplied by the brachial plexus.

The leg is as strongly affected as the arm. When lying on his back in bed we notice prolonged spasm of the extensors and flexors of the toes, the flexors however generally prevailing. Thus the foot is extended and the toes strongly flexed, though still the extensor muscles are hard, and their tendons to the toes stand out like strong tight cords. The extensor of the great toe is especially contracted, and produces a curious deformity; the last phalanx of this toe being strongly flexed, but the first rather extended. Remaining in this state a few minutes, the toes being rigidly fixed, there occurs a rapid, almost vibratile movement of slight extension and flexion in the great and second toes. After this has lasted a few seconds the flexor of the great toe appears to relax, and the extensor draws it up, so that it stands almost at a right angle to the dorsum of the foot, the other toes remaining flexed; then in a few seconds the great toe itself again becomes flexed.

In addition to these contortions, under excitement or voluntary movement in any part of the body, the foot becomes strongly inverted, or less frequently everted. Sometimes the whole leg is rotated inwards, at other times rotated outwards. When made to walk the movements became still more extensive, varied, and continuous, justifying much more characteristically the name athetosis. When walking the movements of the right leg are stiff. The knee is generally a little flexed, and the limb slightly rotated outwards. At one time he plants only the toes

and the pad behind them on the ground, then in a few seconds he walks on the heel, then on only the outer part of the foot, and again the foot becomes strongly everted, so that he walks on its inner part, these differing postures repeatedly following each other. Sometimes the thigh becomes much more flexed; and during walking all the leg and thigh muscles feel hard, and seem to be partly contracted, thus rendering his walk stiff and constrained. While walking his arm is almost always strongly extended behind his back, being rotated sometimes inwards, at other times outwards.

Voluntary action considerably increased the movement both of arm and leg; the increase being much more marked in the limb voluntarily moved. Thus, walking greatly increases the intensity and extent of the arm movements, and voluntary action of the arm increases the leg movements. Some acts seem particularly to excite the movements, for instance, acts requiring fine adjustment and complex combinations, as writing. On being told to write his name, on taking the pen between his thumb and two forefingers some seconds elapse before he can begin, and then by a strenuous effort he begins his name, the lines being very tremulous, from the strong spasm which he can only partially control. Before finishing his name he was obliged to stop several times, and on each occasion he experienced increased difficulty in renewing the attempt. In trying a second time his difficulties were much enhanced through the augmented intensity of the spasm, and sometimes the arm became fixed, and could not be moved a bit; at last the spasm of the whole forearm and hand became so marked that he could write no more. Whilst this was going on there was increased spasm in the foot and leg; the spasms in these members becoming much more intense, and at last involving some of the thigh muscles. The effect on the great and second toe was very curious, both at first being powerfully flexed, but the first phalanx of the great toe was extended so as to suggest a claw-like appearance. In a short time both toes became affected for a while with a rapid though limited flexion and extension movement, and then the great toe became strongly extended.

Voluntary movements of the healthy left side considerably increase the movements on the right side, though less than

voluntary movements of the affected side. Thus when told to write with the left hand, this action greatly increased the movements in the right arm and leg; and on being told to move the fingers quickly on a board, as if playing on a piano, the attempt induced still greater movements in the damaged side. When told to write with his healthy (left) hand, he took the pen, but could move neither arm nor hand; and he used the curious and suggestive expression, that "it seemed as if the other side kept back the hand." To us it seemed as if the force set free by the voluntary effort was diverted, as it were, from its intended destination, and ran into the central nervous structures controlling the right arm and leg, producing increased movement in those parts.

Emotional excitement increases the movements in the right limbs "more," as the patient remarked, "than anything else," more even than voluntary acts; thus, if startled or suddenly awakened, the movements became excesssive. When crossing a street, if a cab came quickly down on him, impelling him to hurry, the movements became greatly aggravated, and "to save his life he couldn't move;" and this, it should be remembered, although he retains full use of his left limb, and can hop well on the left leg. Here, too, it seems that all the force set free in the voluntary effort to move is diverted from the left side, and runs into the right side, producing in its muscles uncoordinated and spasmodic action.

Sometimes when excited the right leg is strongly drawn up, so that he is obliged to stand on one leg.

Spasmodic contractions also are produced, and are increased reflexly. Pinching or pricking the skin with a pin does not, it is true, produce the contraction, but on extending a contracted muscle it instantly recontracted far more strongly. Thus, when I extended one of the flexed fingers or toes the *whole* of the flexor muscles of the right side became far more powerfully contracted without complicating any other muscles. Moreover, some muscles, even when uncontracted by spasm, become contracted on attempting to straighten them. Thus the superficial flexor of the arm was often powerfully contracted, the deep one remaining relaxed; hence the middle phalanx of the finger was tightly pressed in the palm whilst the last phalanx remained

flaccid. On pulling the last phalanx of one finger away from the palm the deep flexor contracted, whilst all the terminal phalanges were strongly pressed on the palm.

Warmth increases the movements considerably. The limbs, says the patient, are in summer more sharply contracted, and the movements are more frequent and more incoherent. Mr. Bury placed the right foot into a bath of hot water, and its muscles soon began to contract violently, the foot being inverted and everted with great force, the man describing "it as ten to one worse." After the removal of the foot from the hot water the aggravation persisted some time. On another occasion I forced the left foot in hot water, so hot indeed that at first it gave him pain, so that the emotional condition thus induced certainly increased the movements. However, on reducing the water to a comfortable temperature, the movements, if at all, were very slightly increased; the man himself thought they were a trifle. Warmth to the right foot very decidedly increased the movements in the right arm, but as the contraction of the right leg caused considerable pain, possibly the arm movement was due to this circumstance.

The hurtful influence of heat is further exemplified when the sun falls across his shoulders; then, he says, the arm shoots above his head, and if by a strong voluntary effort, or with the aid of the other arm, he pulls down to his side the upraised limb, when the hold is released, or the voluntary effort is exhausted, back it flies immediately to its former posture. Whenever, he says, the warmth of the sun is on his back it produces difficulty of breathing "from want of movement of the right side of the chest;" whence it is probable that the muscular contractions sometimes invade the right side of the trunk, and I may add here that during a deep inspiration I find by measurement that the left expands considerably more than the right side.

When standing with his eyes shut he says "all the time I am thinking of my right side, lest I should fall;" though when engaged in conversation, so that he forgets himself, the movements are not increased, nor does he seem at all unsteady. Walking, however, with his eyes shut much increased the spasm. "The limb," he says, "is stiffer;" in fact it is very apparent that voluntary movement under these circumstances becomes far more

difficult and limited, but the disability passes away when he opens his eyes.

During the early part of the attack he states that the movements were greater during sleep than when awake, but this is not now the case, for careful watching at night has detected no movement of the right side. On examining his hand during his sleep both Mr. Bury and I have found it a little flaccid, with the fingers a little flexed, but immediately he wakes spasm seizes both hand and foot.

He has paroxysmal exacerbations occurring sometimes twice or three times a week, sometimes delayed a week, and then they are always very severe. These attacks last three or four hours, correspond in all respects to those described a little further on, induced by the subcutaneous injection of strychnia. These attacks are generally precipitated by some emotional disturbances, and for a day or two afterwards the movements are less severe.

The involuntary contractions do not cause any sensation of tiredness, though voluntary movements of the right side soon weary him.

There is no permanent rigidity of any muscles of the right extremities.

There is no loss of sensation, tactile or painful, in the right side. The "muscular sense" is also intact. There is no hypertrophy of the muscles of the right side. The left side is quite normal.

On January 30th we injected $\frac{1}{25}$th gr. of sulphate of strychnia into the calf of the left leg without any apparent effect. Subsequently, on three occasions, we repeated the injection at intervals, $\frac{1}{16}$th gr. into the left leg, and $\frac{1}{16}$th and $\frac{1}{30}$th gr. into the right leg, and in each instance the injection induced great increase in the movements, the left side remaining unaffected. In fact the strychnia produced in the right side convulsive movements identical with those described by Dr. Ferrier as arising from electric stimulation of the corpus striatum. It is better, I think, now to give the notes of his condition taken at the time by my assistant, Mr. Bury, and by myself. On giving the first injection, January 31, the pulse was 108 and the respiration 30. Immediately afterwards

the movements became more active, and in a quarter of an hour the limbs were in constant movement, the contraction of the muscles being very powerful, some seconds elapsing before they relaxed and another set became contracted. The breathing was hurried and panting. He complained of great pain in his limbs and of dry mouth, pulse 124, respiration 52. In fifty minutes violent spasms of the right leg set in, and, he said, the muscles felt as if they were torn. In one hour and a quarter there was slight opisthotonos and pleurosthotonos. Breathing very hurried, pulse 140. The movements, with the exception of the pleurosthotonos and opisthotonos, were not at all tetanic, but a very great aggravation of those habitually present. Three hours after the injection I found him a little better, each contraction being shorter, and the muscular movements were more rapid. He complained of great faintness, and looked anxious. *The movements were then quite continuous, the limbs never keeping in any position more than a few seconds,* and all the muscles of the limbs being in turn attacked. *It was at this time a genuine case of athetosis after Hammond's original description,* though the muscles involved were more numerous and the movements much stronger. He complained of great difficulty in breathing, saying "he could only just fetch his breath;" there was no duskiness, but it was evident that he had to breathe voluntarily, and with some effort. The respiratory muscles of the right side were evidently affected. I asked if he had been ever so bad before. He said, "Oh yes, I am like this in the hot weather, and have the same difficulty in breathing." In four hours he had recovered from the effects of the strychnia.

The following notes were taken by my assistant, Mr. Morshead. *February 7th,* 10 A.M.—Patient's movements this morning were a little excited, and he complained of a sense of impending shortness of breath. 11 A.M. We injected into the right calf a solution of about $\frac{1}{15}$th of a grain of strychnia. Pulse 90; respiration 30 per minute. Within five minutes after the injection the movements were distinctly increased. At twenty minutes the first attack of opisthotonos occurred, the back becoming distinctly arched. The movements of the right limbs were like those habitually present, only greatly exaggerated. The arm and leg were not equally affected at the

same moment—whilst the one was violently convulsed, the other became comparatively quiet, the movements of the right limbs thus alternating. Adduction and flexion were the most powerful movements. Subsequently the condition was more one of pleurosthotonos, the body becoming arched, with the concavity towards the right side. At no time was anything more than some slight tremor observed of the left limbs. There was no working of the facial muscles of either side. The skin was covered with sweat generally, but no unilateral sweating was observed. During some of the more severe spasms the respiratory movements of the right chest were much diminished. The respirations were not increased in number. Musical cooing râles were present over the whole chest during the height of the attack. No cyanosis. The pulse went to 120. The presystolic thrill became more marked, and the double mitral murmur was intensified. There was no priapism. The movements and spasms reached their climax about 12.30 ($1\frac{1}{2}$ hour after injection), and then gradually subsided, and at 1.30 the condition of the patient was pretty much the same as before the injection, the râles having quite gone. During the afternoon the patient seemed a good deal exhausted, and felt much stiffness in the knuckles and ankles.

8th.—Had a good night. At 11 A.M. $\frac{1}{25}$th gr. of strychnine was injected into the right calf. Pulse 90. In about five minutes the movements increased as yesterday, but were by no means so violent. The pulse went to 126. No râles heard.

9th.—Whilst preparing to give a hypodermic injection of $\frac{1}{30}$th gr. of strychnine into right calf, the movements became greatly exaggerated, and after the injection continued to increase rapidly. The pulse at the time of injection was 90; respiration 36. Opisthotonos occurred first as before, and was followed by frequent attacks of pleurosthotonos. These latter were far more severe than on any previous occasion. The body was strongly curved over the right side of the bed (concavity towards the right side). Sometimes the right side of the body would be jerked up, so that the patient rested entirely on his left side, meanwhile uttering a sharp, involuntary cry, the arm and leg being violently extended. The longest tonic spasm observed lasted five seconds, clonic movements occurring in the interval before the next.

In other respects this attack resembled the last, except that no râles were heard. The pulse went up to 126, and respiration to 60. There was no blueness of lips.

As strychnia hypodermically given produced these curious effects, and as in chorea many authorities locate the disease in the portions of the brain probably affected in this man—moreover, as the symptoms in athetosis are so similar to those of chorea—we were led to test the action of strychnia, given hypodermically, on two choreic patients. We made four experiments on them, giving $\frac{1}{25}$th, $\frac{1}{17}$th, and $\frac{1}{12}$th of a grain of the alkaloid, but without producing any aggravation of the movements.

Samson took steadily one minim of liquor strychniæ three times a day till the present time, June, and has greatly improved. Whereas previously he always kept his bed, because on sitting up the movements became intolerable, he now sits up daily, and can walk with comparative ease. The movements are much less marked, and he has far greater control over both the hand and arm.

It will be observed that this case confirms most of the conclusions arrived at by my colleague, Dr. Gowers, and recorded in his excellent paper. It differs however in some respects. As in his cases, voluntary effort increased the spasm. An effort to overcome the spasm by passive force increased it; it ceased during sleep, at all events latterly. But unlike Dr. Gowers' cases, in this man the affection was certainly equally severe, if not more severe, in the leg than in the arm, and no paralysis remained in this member. Warmth increased the spasms.

Charcot says that closure of the eyes does not increase the spasm, but with this patient the contrary happened. The case, however, accorded with Charcot's experience in being associated in the earlier part of its course with hemi-anæsthesia.

Seat and Nature of the Disease.—Dazzling before the eyes, dimness of sight, giddiness preceding loss of consciousness, and followed by loss of speech, and sensation and motion of the right side, point conclusively to the left hemisphere of the cerebrum as the seat of disease. The giddiness indicates the mesencephale, the loss of speech the posterior part of the third frontal convolution, the loss of sensation the thalamus opticus, and the loss of

motion the corpus striatum, as the parts probably affected. As speech returned before sensation, and sensation before voluntary motion, the main stress of the disease must have fallen on the corpus striatum, and in a less degree on the thalamus opticus. It is probable, I think, that the cause of the attack was an embolon, set free from the diseased mitral valves, blocking the middle cerebral artery.

When the patient came under our care the chief effects of the disease had passed away; or rather they had undergone a complete change; for instead of paralysis we had in its stead a state of "mobile spasm," dependent on change in the corpus striatum, or thalamus opticus, but probably on the corpus striatum. It is highly improbable, I think, that the disease is situated in the "cortical centres" of Ferrier, but with more likelihood, as I have said, in the automatic centres at the base, for emotional stimuli, automatic movements, like walking, buttoning the wristband, &c., and purely reflex stimuli, all produce the spasms.

I may next remark that the disease does not imply destruction of function, there being no paralysis, but rather a perversion of function.

In this case we have the following four circumstances to consider:

1. There is, when awake, continuous evolution of force.
2. Incoordinate action.
3. Excessive evolution of force from normal stimuli of will, emotion, and reflex irritation.
4. This evolution of force is produced by stimuli which normally ought not at all to affect this part of the nervous system.

What is the nature of the change in this automatic centre? The most striking symptom is incoordinated action. Any stimulus originating either in the will or in the emotional centres no longer calls forth a definite and coordinated act, but on many occasions, and always, after a time, an utterly purposeless act. Yet it is something more than a mere incoordination; for assuming that for every complex combination of muscular contraction there is a coordinating centre, the disease does not consist merely of a destruction or weakening of some of these

centres, for then we should get only irregular (incoordinated) action of the muscles set in motion by the voluntary act, but in addition to these many other muscles became powerfully affected; muscles even in the limb not set in motion by the will. Thus the stimulus, whether voluntary or emotional, does not run along definite channels, but radiates in all directions throughout the diseased area of gray matter, producing disorderly movements; in other words, that force or condition of the nervous centres which restrains the discharge within certain definite areas of the gray matter is weakened, and, owing to this diminished resistance, the stimulus radiates into other parts, producing disorderly and widespread movements.[1]

As in the case of allied spasmodic diseases, as chorea, strange to say, stimuli directed to the diseased nervous tissue not only produce disorderly movements, but impressions directed to a wholly different part find their way to the diseased gray matter, and radiating throughout it, produce disorderly movements. For instance, a voluntary stimulus intended to contract a part of the healthy arm or leg is partly or even wholly diverted to the diseased portion, and sets free in it a nervous discharge instead of in the part it was intended for. In this case emotional stimuli were more diverted by the diseased gray matter than volitional. We may assume that in this case, through some defect in resistance, impressions are not restricted to their proper channels; but at some point where the resistance fails, the nervous force leaks out, finding its way to the diseased nervous structures connected with the right arm and leg.

Some eminent writers would I believe refer this evolution of force in the diseased nervous centre to higher nutrition reaching an explosive degree; and they would say that in Samson's case an ordinary volitional or emotional stimulus liberated an unusual amount of force, producing very powerful muscular contraction. It appears to me there are cogent objections to this view. We have seen that voluntary movement increases the incoordinated movement, and the longer the voluntary movement

[1] This view coincides with the one advanced by Dr. Gowers in his paper. He says, "The slow, irregular spasm which occurs on movement is clearly due, in part, to a diversion of the motor impulse, along an unintended path, or its irradiation over a wider region than that to which it should have been confined."

continues, the greater the incoordinated becomes, till at last incoordinated completely usurps coordinated movement. Now according to the foregoing theory, the voluntary movement should, so to speak, work off the higher nutrition, and keep it down below an explosive point, and the longer the persistence of the voluntary movement, the more the nutrition (potential force) is consumed, and the incoordinated should give way to co-ordinated action. On the supposition that the lesion has lessened and in some parts destroyed the resistance, the last described effect of voluntary movement is easy to explain. If depressed then, only by voluntary action it becomes still further depressed, and hence the impulse can more readily irradiate. The condition is comparable to that of the spinal cord of a frog to which a dose, only just sufficient to produce tetanus, has been given. On irritating a limb we produce at first only a coordinated reflex act, but by keeping up the reflex contraction of the leg this at last becomes tetanic. The strychnia has depressed resistance, though not enough to permit the onset of tetanus till resistance itself is still more depressed by the functional activity of the cord. If it is said, How then do you explain the excessive evolution of force, and consequently very powerful muscular contraction?—this I would explain by adducing a fact I have tried experimentally to prove in conjunction with Mr. Murrell, that the resistance not only localises, but restrains the amount of nervous discharge, and by weakening it we not only allow the irritation to irradiate, but also to set free an excessive amount of force.

Is any of the spasm in Samson's case due to the lesion which produced the loss of resistance? Does the lesion act as an excitor causing a perpetual discharge of force, or is all the spasm due to volitional, emotional, and reflex stimuli? In the early stage of the case, when the movements were violent during sleep, I suggest that the lesion acted as a stimulus, since it is evident that the movements could not be produced during sleep by the will or by the emotions. Latterly, and during the time he has been under our charge, the original lesion appears to play no part in the evolution of force, for the limbs are quiet during sleep. It is true he tells us that occasionally his arm or leg moves during sleep to wake him; but after careful watching we have never

seen this; therefore it must occur but seldom, and I suggest that it is then due to the emotional excitement of a dream.

It seems to me that athetosis is allied to many diseases, with which at first sight it would appear to have little or no affinity. In athetosis, as we have seen, a change takes place in certain parts of the cerebrum, especially in the basal ganglia (optic-thalamus and corpus striatum), whereby a stimulus is not restrained to its normal portion of gray matter, but "radiates" into other parts, so that instead of coordinated we get incoordinated muscular contraction. In addition, stimuli destined for another part of the brain are diverted as it were to the diseased area; and hence the diseased area becomes excited by stimuli which naturally would exert no action on it. In the case of many other diseases we meet with precisely the same unrestrained action, due to lessening or destruction of the "resistance" in certain portions of the cerebral nervous system, so that impressions radiate beyond their normal sphere. Wherever this irradiation or loss of "resistance" occurs, the change causing it, I venture to assume, is identical, whatever the kind of disease leading to it; being in the present case probably embolism. If this view holds good it is obvious that athetosis becomes connected with many diseases manifesting symptoms widely different from those pertaining to athetosis itself. If the "loss of resistance," or in other words, the condition permitting "irradiation," is situated in parts connected with motor nerves, we get irregular incoordinated contraction of muscles; if with parts connected with sensory nerves, we get widespread pains. The persistence, remittence, or intermittence of the exciting cause will of course modify the symptoms. Thus if the exciting cause is permanent, then the muscular contraction or pain will be permanent; if remittent, the contraction or pain will be remittent; if intermittent, then also the contraction or pain will be intermittent.

Thus the name athetosis indicates the seat of the disease rather than its nature.

The constant slow movement due to the consecutive slow contraction and relaxation of different muscles can, I think, be explained in this wise: the loss of resistance being partial only, as soon as the evolution of force has reduced the potential

orce, the remaining resistance is adequate to restrain the irradiation, till nutrition has again restored and accumulated the potential force, so that the weakened resistance, unable longer to restrain the evolution of force within normal limits, contraction and relaxation of various muscles will then occur with consequent constant changes of the affected limb.

The similarity between athetosis and chorea is too evident to be dwelt on; so I will now attempt to show its affinity to diseases with which at first sight it would seem to have no relation. For example, it appears to me to be allied to stammering. In stammering, before the word can be uttered, there occurs, in mild cases, remittent and alternating spasm of the muscles surrounding the mouth; in more determined stammering almost all the muscles supplied by the seventh nerve are affected; in severer cases the neck muscles produce frequent spasmodical jerking of the head; whilst in very severe cases, in addition to all these muscular movements, there is frequent spasmodic heaving of the shoulders.

On analysing these movements, we find that the impulse, starting from the speech centre, instead of running at once in its proper channels, is diverted, and through loss of resistance radiates through the nucleus of the seventh, the irradiation being in mild cases slight, and involving that part only of the nucleus supplying the muscles surrounding the mouth. In more developed cases, however, irradiation takes place throughout the greater part of the nucleus of the seventh, and in still severer instances involving the thin gray matter in connection with nerves supplying some of the neck muscles, and reaching even the spinal accessory, causing spasmodic contraction of the trapezius and consequent heaving of the shoulders. As in athetosis, so in stammering, the muscles are not all simultaneously contracted, some being relaxed, whilst others are contracted. This state is not, of course, continuous like athetosis, for the simple reason that the exciting cause, speech, is itself intermittent; but I venture to think that the condition (the loss of resistance) permitting the irradiation is the same, only that it affects different parts, and stammering might therefore be called intermittent athetosis of the facial muscles.

I will give another illustrative example in the case of a man

belonging to a family of stutterers, himself when young a notable stutterer. After a time the spasmodic movements of the face and of the head ceased, leaving in their stead a spasmodic shrugging of the right shoulder three or four times repeated before he could begin to speak, when the shoulder became quiet. Like ordinary stammering, the convulsion was much more marked, indeed was almost violent when he tried to pronounce C and Z. Whilst the shrugging was going on he meanwhile was obviously striving strenuously to get out the word or letter. Here, the defect permitting irradiation, the loss of resistance, at first extensive, gradually grew less; but instead of disappearing entirely, as in most cases, a remnant remained, the impulse generated in the act of speech irradiating to the nucleus of the *right* spinal accessory nerve.

Athetosis is allied also to painful spasmodic affections, as neuralgia. But here the irradiation occurs in a portion of the gray matter associated with sensory nerves. Indeed, in watching over a case of athetosis we were struck with its similarity to aneuralgia. Thus we might compare it to a case of sciatica. In sciatica there is often some persistent pain, and in our case there was some sustained spasm. In sciatica, in addition to the characteristic persistent pain, other pains shoot now through one branch of the nerve, now dart through another. So with athetosis; in addition to the sustained contraction we get likewise now contraction of one set of muscles, and these relaxing, then contraction of another set.

It may be objected that in athetosis the irradiation is comparatively tardy, as shown by the slow continuous movement, whilst in stammering it is far quicker, and in neuralgia is of lightning-like rapidity; and that this difference must imply a difference in the nature of the change permitting the irradiation. To this I may answer that the rapidity of movement varies greatly in athetosis, as shown in the cases reported by Dr. Gowers; in other diseases the rapidity with which the nervous discharge travels varies greatly; thus the aura of epilepsy and the allied aura in other nervous affections vary much in the rate of passage along the central nervous system, yet we do not therefore assume that the nature of the change in the nervous centres is different in kind.

THE PRACTITIONER.

SEPTEMBER, 1879.

Original Communications.

NOTES OF A POST-MORTEM EXAMINATION ON A CASE OF ATHETOSIS.

BY SYDNEY RINGER, M.D.,

Professor of Medicine at University College, London.

In the *Practitioner* for August, 1877, I published the notes of a case of athetosis. The patient, when twenty-eight years of age, was struck down with right-sided hemiplegia, hemianæsthesia, and unilateral sweating. He subsequently recovered the lost power and sensation on the right side, but the unilateral sweating persisted. As he regained his lost power the athetosis developed itself. The patient was re-admitted May 29, 1878. He now suffered severely from his heart; he had orthopnœa; his jugulars were full, and his lips and ears livid, his legs were greatly swollen, and his expectoration bloody. His athetosis was much the same as when he left the hospital about a year before. He died June 12. I shall first give a brief account of the examination of his heart and lungs, and then a fuller account of the state of his brain.

The right auricle and ventricle were very greatly enlarged, and the auricle much hypertrophied, its walls being twice their

natural thickness. The tricuspid valves were diseased and partially united at their edges, so as to cause decided tricuspid obstruction. The pulmonary artery contained an old laminated clot occupying a large part of the lumen of the vessel. The left auricle contained a small old clot in the appendix. The mitral valve was much constricted, and would only admit the tip of the forefinger, and the edge of the valve-ring was calcareous. The left ventricle was very slightly hypertrophied. The aortic valves were not quite competent, and showed slight calcareous change. The heart weighed twelve ounces. In both lungs we found pulmonary apoplexies. The walls of the pulmonary artery had undergone considerable atheromatous and calcareous degeneration.

Brain.—We could not discover any trace of an occluded vessel.

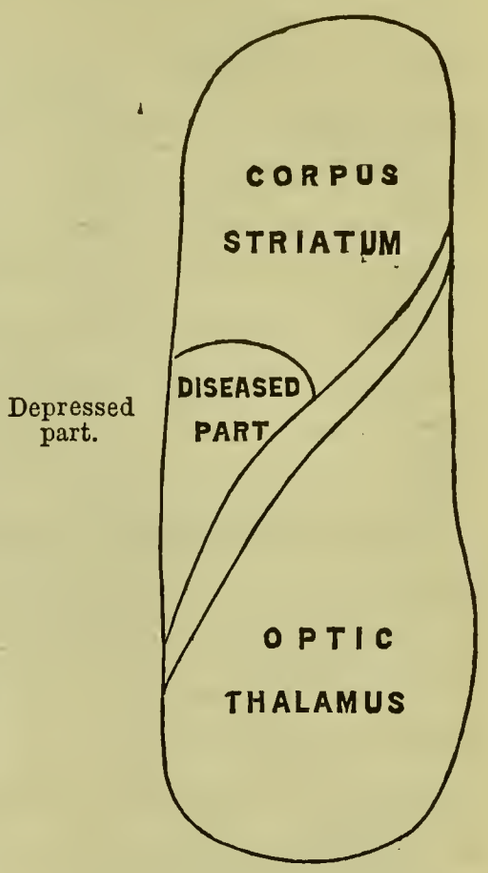
The pia mater was slightly opaque and cloudy, perhaps rather more on the left than the right side, and especially so anteriorly.

The left hemisphere did not seem at all wasted. There was, perhaps, a little wasting over a very small extent, an inch in diameter, and an inch outside the longitudinal fissure and at the junction of the anterior and middle third. On stripping off the pia mater the convolution of the left side seemed to fall apart a little more than those of the right.

We then made transverse horizontal sections across the brain, and found the brain substance, judging by the naked eye, healthy till we laid bare the lateral ventricles. The parts in the right lateral ventricle looked quite healthy. In the left lateral ventricle there were evident signs of disease affecting the posterior part of the corpus striatum, that portion close to the tænia semicircularis, and which lies just outside the anterior portion of the thalamus. This part was depressed and rather hollowed out, and the membrane covering it was thickened. The anterior part of the corpus striatum and the tænia semicircularis looked healthy. The left optic thalamus was decidedly smaller and flatter than the right.

We then exposed the third ventricle and found the anterior and posterior commissures very distinct, but the soft commissure was gone. The optic thalami were now better exposed, and the

diminution of the left was now more apparent, it being perhaps a quarter less than the right, the transverse measurement of the right thalamus being two and a half centimetres, that of the left two centimetres. We then made transverse vertical sections through both corpora striata. The first section was made through the anterior part of the corpora. We found the brain substance beneath the depressed portion of the left corpus much softened, the softening extending a little to the right and left of the depression. The softened tissue was a light yellow colour.



We then made another transverse section a quarter of an inch posterior to the first, and this exposed, on the left side, the anterior part of a cyst situated in the grey matter of the lenticular nucleus, just external to the white matter dividing the caudate from the lenticular nucleus. Further sections showed that this cyst had its long axis in the antero-posterior measurement of the brain and involved the lenticular ganglion, the anterior part of the cyst being mainly, if not exclusively, in the lenticular ganglion, but it extended behind the corpus striatum, lying outside and rather below the left thalamus, the posterior limit of the cyst reaching to one and a half centimetres anterior to the posterior edge of the optic thalamus. The cyst was external to the thalamus, half a centimetre of white matter intervening between the cyst and the grey matter of the thalamus. Thus, posteriorly, the cyst was situated in and surrounded by the left peduncular expansion. Close to the posterior part of the corpus the cyst was only a quarter of a centimetre from the grey matter of one of the convolutions.

The cyst measured transversely one and a half centimetres, and its long measurement was about three centimetres.

The cavity was lined by loose connective tissue containing

serosity, and the tissue around the cavity was tinged a light orange colour.

The cyst, in general terms, lay anteriorly in the corpus striatum, being situated in the lenticular nucleus; behind it lay outside, and rather below the anterior two-thirds of the thalamus, but the posterior portion of the whole left corpus was softened, and the thalamus was wasted.

The parts posterior to the lesion, namely, the crus, the pons, the medulla, the floor of the fourth ventricle, and the spinal cord and nerves, were carefully examined, but no evidence of wasting, or any other change, could be detected by the naked eye.

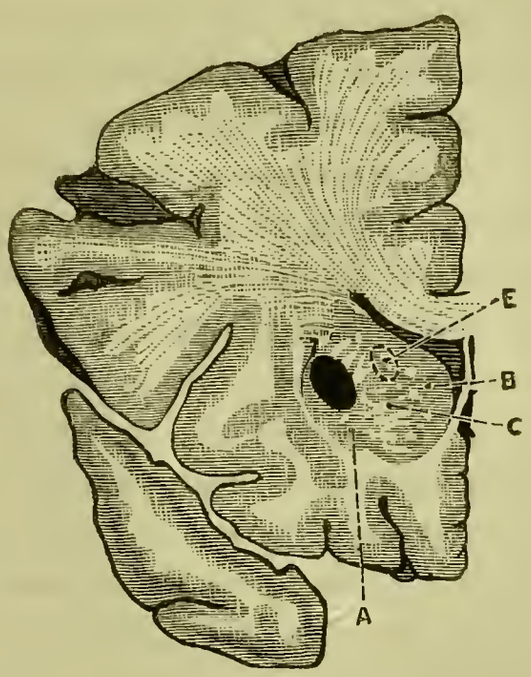
Dr. Ewart kindly took charge of the brain, and has made a careful microscopical examination which I append. He also has given me an account of the situation of the cyst and has kindly made the drawing showing its position. He says "the cyst lies in the posterior half or two-thirds of the lenticular nucleus, the cyst lying in front immediately without the inner capsule, but passing obliquely through the lenticular nucleus. After leaving the posterior part of the lenticular nucleus it involves the whole of the white matter lying outside and rather beneath the optic thalamus, and runs parallel with the left thalamus for about half an inch. A small portion of the grey matter of the optic thalamus adjacent to the cyst is destroyed."

I now give the drawings prepared by Dr. Ewart. The first represents a transverse section through the anterior part of the left corpus striatum, the second through the posterior portion, and the third through the optic thalamus.

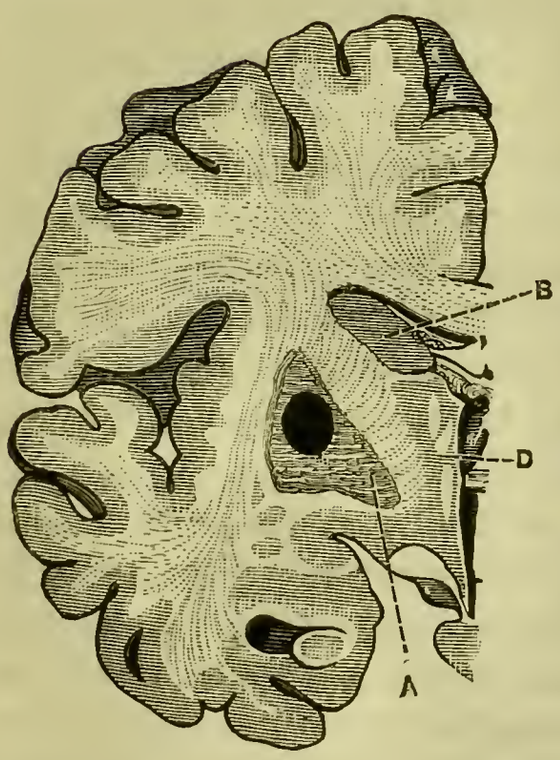
"*Microscopic Appearances presented by Transverse Sections through the Structures surrounding the Anterior Third of Cyst.*—The most striking appearance presented by sections through the anterior end of cyst was the projection into its interior of fibres derived in part from the inner capsule (Fig. 1, C), but chiefly from the lenticular nucleus (Fig. 1, A). A few of the fibres extended in a straight line for 2—3 m.m. towards the centre, but the greater number formed an irregular network, supported by the empty blood-vessels, immediately within the cyst. In the meshes of this network were nerve-cells, blood-corpuscles and pigment masses. On the inner side many of the

fibres were traceable to the inner capsule, some passing towards the surface, others towards the spinal-cord. At the lower and outer side the fibres were more delicate, and many of them from

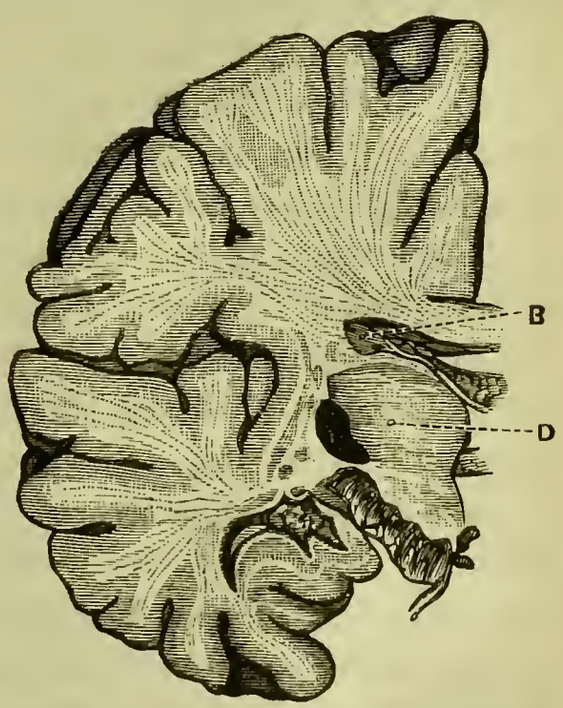
1.



2.



3.



their connection with small round and oval nuclei were connective tissue-fibres, whilst others from their connection with large nerve-cells were evidently nerve-fibres. Other fibres passing from the peduncular expansion either entered to end in the cyst or passing along its outer side communicated with cells from which processes entered the cyst. The greater number of

the fibres radiating from the cyst were lost sight of in the substance of the lenticular nucleus. Lying on and between the nerve- and connective tissue-fibres were many small round and oval nuclei, a few blood-corpuscles, and in several sections large oval (in transverse section round) sacs packed full of red blood-corpuscles. These sacs had probably resulted from the reflux of blood from the surrounding healthy substance into thin and unsupported veins. They were never found at the side of the cyst next the inner capsule. The arteries were empty and served as a supporting framework for connective tissue and nerve-fibres which had escaped the softening process; the nuclei in the walls of the vessels were very distinct but apparently healthy."

"To pass now to the ganglionic nerve-cells, and first those lying isolated or in groups amongst the fibres lining the cyst. A number of them looked quite healthy and had either long or short processes in connection with them, some of which passed to cells lying in the substance of the nucleus. From such cells in which the only visible change was a slightly granular condition of the nucleus to those of which scarcely anything but a coarsely granular nucleus was left, every possible gradation existed, the amount of degeneration being in ratio to the distance from the healthy structures. While the first appearance of atrophy seems to be a granular condition of the nucleus, the protoplasm around the nucleus seems first to undergo complete disintegration. Many of the cells adjacent to the cyst, and from which processes passed to its interior, had so atrophied that they would in all probability be functionally useless, but the cells external to these had large bright nuclei and nucleoli, and the processes passing to and from them were larger than usual. This apparent hypertrophy of the cells and fibres connected with them may be accounted for by supposing that besides their own work, they had done at least part of the work of the cells and fibres which had been destroyed."

"*Sections through the Middle Third of the Cyst* (Fig. 2) presented similar appearances, but on account of its lying deeper in the substance of the ganglion its relation to the inner capsule and the peduncular expansion was less apparent. The nerve-cells were similar to those already described, but less numerous, and the degenerative changes penetrated further into the centre

of the ganglion. Numerous small bundles of nerve-fibres ended abruptly in the cyst and were surrounded with connective tissue-fibres and cells, blood-corpuscles, and pigment."

"*Sections through the Posterior Third of the Cyst* (Fig. 3) were especially interesting, for at this part the cyst had all but left the lenticular nucleus to involve the outer and lower surface of the optic thalamus and the fibres of the outer capsule lying between it and the claustrum."

"Numerous very delicate nerve-fibres extended into the cyst from the thalamus, and along with them, as before, connective tissue-fibres and blood-vessels. There were no widely dilated veins, but many isolated red blood-corpuscles. The nerve-cells in the irregular lining of the cyst as well as those in the substance of the thalamus were less distinct than in the other sections, and it was almost impossible to make out their relation to the healthy and partly-destroyed fibres. The fibres on the outer side of the cyst, however, were apparent enough, and the ruptured and degenerated fibres passing from it were traceable for some distance in both directions. From two to four millimetres of the grey substance of the thalamus round the cyst had lost its normal appearance, many granules were present, the fibres were indistinct, and the cells faintly granular."

"*Changes in the Caudate Nucleus.*—Near the inner capsule and parallel to the depression on the surface of the caudate nucleus already mentioned a tract of grey matter was found in which atrophic changes had evidently set in. The intercellular substance had partly disappeared, the cells almost obscured by free blood-corpuscles, and granules were lying near each other, and the fibres passing to and from them were evidently in an unhealthy state. The above changes only existed in the part of the caudate nucleus corresponding in extent to the anterior fourth of the cyst; their position is indicated at E, Fig. 1."

"The fibres and cells of the claustrum and of the other parts of the left hemisphere near the basal ganglia and on the surface were normal in appearance."

"No change could be detected in the spinal-cord, and there was only doubtful evidence of slight atrophic changes in a few of the fibres of the anterior pyramid in sections below the locus niger."

From the above it will be evident that a few of the motor fibres (inner capsule) passing between the lenticular and caudate nucleus and a greater number of the sensory fibres (outer capsule) passing from the filament were destroyed; that about one-sixth of the grey matter of the lenticular nucleus and a small portion of the lower and outer part of the optic thalamus was also completely destroyed, and a portion of what remained of these nuclei and of the caudate nucleus partly atrophied, and further that the fibres passing to and radiating from the destroyed grey matter would be rendered inactive.

The disease in this case therefore appears to have been limited to the optic thalamus, corpus striatum, and the parts just external. The whole of the corpus striatum was much damaged, both the intra- and extra-ventricular portions (caudate and lenticular nuclei). Beside much atrophy and slight degeneration of the intra-ventricular portion, about one-fifth of the lenticular ganglion was destroyed and was occupied by the anterior part of the cyst. A few of the fibres (inner capsule) passing between the nuclei of the corpus striatum were destroyed. The corpus striatum was the part which suffered most, but the left optic thalamus was also wasted, and a small portion of the lower and outer portion of this body was completely destroyed, whilst a considerable portion of the white matter external to the thalamus (sensory fibres of the outer capsule passing from the filament) was destroyed, and the part occupied by the posterior part of the cyst. It thus appears that the diagnosis made when the man first came under my care is (in the main) correct.

In the account published in the *Practitioner* (August, 1877), I said, "Dazzling before the eyes, dimness of sight, giddiness preceding loss of consciousness, and followed by loss of speech, and sensation and motion of the right side, point conclusively to the left hemisphere of the cerebrum as the seat of the disease. The giddiness indicates the mesencephalon, the loss of speech, the posterior part of the third frontal convolution, the loss of sensation, the thalamus opticus, and the loss of motion the corpus striatum, as the parts probably affected. As speech returned before sensation and sensation before voluntary motion, the main stress of the disease must have fallen on the

corpus striatum and in a less degree on the thalamus. It is probable, I think, that the cause of the attack was an embolon set free from the diseased mitral valves blocking the middle cerebral artery."

It will conduce to the better understanding of this interesting case if I here introduce an account given me by Dr. Ewart of the probable course of the nerve fibres.

A considerable number, about one-fourth, of the fibres pass from the crus cerebri to the cortex without being in connection with the cells of the thalamus and corpus, some of the fibres passing outside these bodies.

The motor fibres running along the crusta radiate to all parts of the cerebrum to the frontal, parietal, occipital, and sphenoidal lobes, but especially to the frontal and parietal. One set of fibres passes directly to the occipital and temporal lobes, and another passes between the caudate and lenticular nuclei to the parietal and frontal lobes without any connection with the grey matter of the corpus. The remaining fibres of the crus pass into the grey matter of the corpus and terminate in the cells, and this part is in connection with the fibres which pass to the frontal and parietal lobes, and the apex of the temporal and to the insula. The olivary fasciculus from the anterior column, the fasciculi teretes from the lateral column, and fibres from the posterior pyramid, unite to form the tegmentum from which fibres pass to the corpora quadrigemena, corpora geniculata, and optic thalamus, and proceed from the thalamus to form part of the peduncular expansion and pass to the occipital parietal and tempero-sphenoidal convolutions and the insula. Other fibres undoubtedly pass directly to the cortex.

The consideration of this case naturally falls into two parts :—

1. The period of paralysis.
2. The period of athetosis.

It is interesting to observe that this man recovered completely from paralysis, both of motion and of sensation, although a large hole tunnelled through a most important part of his brain remained, and the tissue around it, especially that composing the left basic ganglia, continued considerably damaged. A not inconsiderable and a highly important part of the left cortex

was therefore permanently cut off from the body and yet no paralysis remained. No doubt both in effusion of blood and in embolism much brain substance around the effused clot or around the tissue deprived of its blood, becomes affected by pressure, serous effusion, &c., and as the pressure is removed, the paralysis due to these causes subside. But in this case a serious lesion destroying a large extent of brain persisted, and yet the patient recovered completely from his paralysis. How is this to be explained? The broken communication by means of the cyst between the cortex and the rest of the body could be re-established in two ways: by vicarious function, parts of the brain taking on function formerly performed by other portions of the brain; or new channels for the passage of the nerve current arrested by the cyst might be formed around it.

This case does not enable me to say which of these views is correct, but I may suggest if the restoration of lost power was due to vicarious function, then that part of the cortex cut off by the cyst and no longer exercised should waste, but we could not distinctly detect any wasting of the convolutions.

I may point out that the lesion was situated in the usual seat in cases of hemianæsthesia and unilateral sweating, that is in the internal capsule outside and just below the thalamus opticus.

This case teaches us much regarding the seat and nature of the change in athetosis.

It is obvious that the cavity in the brain could not be the immediate cause of the incoordinated and involuntary movement of athetosis, for this breach of continuity of the brain could only cause paralysis. The athetosis therefore must be attributed to the damaged tissues in the neighbourhood of this cavity, and must in this case be due to the damage in the optic thalamus, or the corpus striatum, or both.

These are the structures in which one would naturally expect to find the lesions. Dr. Hammond in his original communication suggested the grey matter of the optic thalamus or the corpus striatum as the probable seat of disease.

As regards the nature of the disease, this case shows that it is due to atrophy and degeneration of the basal ganglia.

How does this atrophy and degeneration produce the move-

ments occurring in athetosis? Dr. Gowers in his paper published in the *Medico-Chirurgical Transactions* for 1876, says:—"The slow irregular spasm which occurs on movement is clearly due in part to a diversion of the motor impulse along an unintended path, or its irradiation over a wider region than that to which it should have been confined." "The symptoms point clearly to damage to the grey matter of the brain, to local perverted nutrition of nerve-cells, in consequence of which they over-act either spontaneously or on the stimulus of the volitional impulse which is by their over-action perverted or irregularly distributed."

I beg to add the views I suggested in my previous account of this interesting case:—

The disease in this man does not imply destruction of function, there being no paralysis, but rather a perversion of function.

In this case we have the following four circumstances to consider:

1. There is, when awake, continuous evolution of force.
2. Incoordinate action.
3. Excessive evolution of force from normal stimuli of will, emotion, and reflex irritation.
4. This evolution of force is produced by stimuli which normally ought not at all to affect this part of the nervous system.

The most striking symptom is incoordinated action. Any stimulus originating either in the will or in the emotional centres no longer calls forth a definite and coordinated act, but on many occasions, and always, after a time, an utterly purposeless act. Yet it is something more than a mere incoordination; for assuming that for every complex combination of muscular contraction there is a coordinating centre, the disease does not consist merely of a destruction or weakening of some of these centres, for then we should get only irregular (incoordinated) action of the muscles set in motion by the voluntary act, but in addition to these many other muscles become powerfully affected; muscles even in the limb not set in motion by the will. Thus the stimulus, whether voluntary or emotional, does not run along definite channels, but radiates in all directions throughout the diseased area of grey matter, producing disorderly movements;

in other words, that force or condition of the nervous centres which restrains the discharge within certain definite areas of the grey matter is weakened, and, owing to this diminished resistance, the stimulus radiates into other parts, producing disorderly and widespread movements.

As in the case of allied spasmodic diseases, as chorea, strange to say, stimuli directed to the diseased nervous tissue not only produce disorderly movements, but impressions directed to a wholly different part find their way to the diseased grey matter, and radiating throughout it, produce disorderly movements. For instance, a voluntary stimulus intended to contract a part of the healthy arm or leg is partly or even wholly diverted to the diseased portion, and sets free in it a nervous discharge instead of in the part it was intended for. In this case emotional stimuli were more diverted by the diseased grey matter than volitional. We may assume that in this case, through some defect in resistance, impressions are not restricted to their proper channels; but at some point where the resistance fails the nervous force leaks out, finding its way to the diseased nervous structures connected with the right arm and leg.

Some eminent writers would, I believe, refer this evolution of force in the diseased nervous centre to higher nutrition reaching an explosive degree; and they would say that in Samson's case an ordinary volitional or emotional stimulus liberated an unusual amount of force, producing very powerful muscular contraction. It appears to me there are cogent objections to this view. We have seen that voluntary movement increases the incoordinated movement, and the longer the voluntary movement continues, the greater the incoordinated becomes, till at last incoordinated completely usurps coordinated movement. Now according to the foregoing theory, the voluntary movement should, so to speak, work off the higher nutrition, and keep it down below an explosive point, and the longer the persistence of the voluntary movement, the more the nutrition (potential force) is consumed, and the incoordinated should give way to coordinated action. On the supposition that the lesion has lessened and in some parts destroyed the resistance, the effect of voluntary and reflex movement is easy to explain. If depressed, then, by voluntary and reflex action it becomes still further

depressed, and hence the impulse can more readily irradiate. The condition is comparable to that of the spinal cord of a frog to which a dose of strychnia, only just sufficient to produce tetanus, has been given. On irritating a limb we produce at first only a coordinated reflex act, but by keeping up the reflex contraction of the leg this at last becomes tetanic. The strychnia has depressed resistance, though not enough to permit the onset of tetanus till resistance itself is still more depressed by the functional activity of the cord. If it is said, How then do you explain the excessive evolution of force, and consequently very powerful muscular contraction?—this I would explain by adducing a fact I have tried experimentally to prove, that the resistance not only localises, but restrains the amount of nervous discharge, and by weakening it we not only allow the irritation to irradiate, but also to set free an excessive amount of force.

Is any of the spasm in Samson's case due to the lesion which produced the loss of resistance? Does the lesion act as an excitor causing a perpetual discharge of force, or is all the spasm due to volitional, emotional, and reflex stimuli? In the early stage of the case, when the movements were violent during sleep, I suggest that the lesion acted as a stimulus, since it is evident that the movements could not be produced during sleep by the will or by the emotions. Latterly, and during the time he has been under our charge, the original lesion appears to play no part in the evolution of force, for the limbs are quiet during sleep. It is true, he tells us, that occasionally his arm or leg moves during sleep to wake him; but after careful watching we have never seen this; therefore it must occur but seldom, and I suggest that it is then due to the emotional excitement of a dream.

It seems to me that athetosis is allied in many diseases, with which at first sight it would appear to have little or no affinity. In athetosis, as we have seen, a change takes place in certain parts of the cerebrum, especially in the basal ganglia (optic thalamus and corpus striatum), whereby a stimulus is not restrained to its normal portion of grey matter, but "radiates" into other parts, so that instead of coordinated we get incoordinated muscular contraction. In addition, stimuli destined for another part of the brain are diverted as it were to the

diseased area; and hence the diseased area becomes excited by stimuli which naturally would exert no action on it. In the case of many other diseases we meet with precisely the same unrestrained action, due to lessening or destruction of the "resistance" in certain portions of the cerebral nervous system, so that impressions radiate beyond their normal sphere. Wherever this irradiation or loss of "resistance" occurs, the change causing it, I venture to assume, is identical, whatever the kind of disease leading to it; being in the present case probably embolism. If this view holds good, it is obvious that athetosis becomes connected with many diseases manifesting symptoms widely different from those pertaining to athetosis itself. If the "loss of resistance," or in other words, the condition permitting "irradiation," is situated in parts connected with motor nerves, we get irregular incoordinated contraction of muscles; if with parts connected with sensory nerves, we get widespread pains. The persistence, remittence, or intermittence of the exciting cause will of course modify the symptoms. Thus if the exciting cause is permanent, then the muscular contraction or pain will be permanent; if remittent, the contraction or pain will be remittent; if intermittent, then also the contraction or pain will be intermittent.

Thus the name athetosis indicates the seat of the disease rather than its nature.

The constant slow movement due to the consecutive slow contraction and relaxation of different muscles can, I think, be explained in this wise: the loss of resistance being partial only, as soon as the evolution of force has reduced the potential force, the remaining resistance is adequate to restrain the irradiation, till nutrition has again restored and accumulated the potential force, when the weakened resistance is unable longer to restrain the evolution of force within normal limits. Contraction and relaxation of various muscles will then occur with consequent constant changes of the affected limb.

The similarity between athetosis and chorea is too evident to be dwelt on; so I will now attempt to show its affinity to diseases with which at first sight it would seem to have no relation. For example, it appears to me to be allied to stammering. In stammering, before the word can be uttered, there

occurs, in mild cases, remittent and alternating spasm of the muscles surrounding the mouth; in more determined stammering almost all the muscles supplied by the seventh nerve are affected; in severe cases the neck muscles produce frequent spasmodical jerking of the head; whilst in very severe cases, in addition to all these muscular movements, there is frequent spasmodic heaving of the shoulders.

On analysing these movements, we find that the impulse, starting from the speech centre, instead of running at once in its proper channels, is diverted, and through loss of resistance radiates through the nucleus of the seventh, the irradiation being in mild cases slight, and involving that part only of the nucleus supplying the muscles surrounding the mouth. In more developed cases, however, irradiation takes place throughout the greater part of the nucleus of the seventh, and in still severer instances involves the grey matter in connection with nerves supplying some of the neck muscles, and reaches even the spinal accessory, causing spasmodic contraction of the trapezius and consequent heaving of the shoulders. As in athetosis, so in stammering, the muscles are not all simultaneously contracted, some being relaxed, whilst others are contracted. This state is not, of course, continuous like athetosis, for the simple reason that the exciting cause, speech, is itself intermittent; but I venture to think that the condition (the loss of resistance) permitting the irradiation is the same, only that it affects different parts, and stammering might therefore be called intermittent athetosis of the facial and other muscles.

I will give an illustrative example in the case of a man belonging to a family of stutterers, himself when young a notable stutterer. After a time the spasmodic movements of the face and of the head ceased, leaving in their stead a spasmodic shrugging of the right shoulder three or four times repeated before he could begin to speak, when the shoulder became quiet. Like ordinary stammering, the convulsion was much more marked, indeed was almost violent, when he tried to pronounce C and Z. Whilst the shrugging was going on he meanwhile was obviously striving strenuously to get out the word or letter. Here, the defect permitting irradiation, the loss of resistance, at

first extensive, gradually grew less; but instead of disappearing entirely, as in most cases, a remnant remained, the impulse generated in the act of speech irradiating to the nucleus of the right spinal accessory nerve.

Athetosis is allied also to painful spasmodic affections, as neuralgia. But here the irradiation occurs in a portion of the grey matter associated with sensory nerves. Indeed, in watching over a case of athetosis we were struck with its similarity to a neuralgia. Thus we might compare it to a case of sciatica. In sciatica there is often some persistent pain, and in our case there was some sustained spasm. In sciatica, in addition to the characteristic persistent pain, other pains shoot now through one branch of the nerve, now dart through another. So with athetosis; in addition to the sustained contraction we get likewise now contraction of one set of muscles, and these relaxing, then contraction of another set.

It may be objected that in athetosis the irradiation is comparatively tardy, as shown by the slow continuous movement, whilst in stammering it is far quicker, and in neuralgia is of lightning-like rapidity: and that this difference must imply a difference in the nature of the change permitting the irradiation. To this I may answer that the rapidity of movement varies greatly in athetosis, as shown in the cases reported by Dr. Gowers; in other diseases the rapidity with which the nervous discharge travels varies greatly; thus the aura of epilepsy and the allied aura in other nervous affections, vary much in the rate of passage along the central nervous system, yet we do not therefore assume that the nature of the change in the nervous centres is different in kind.

ON THE RELATIVE ACTION OF DUBOISIA AND ATROPIA.

BY SYDNEY RINGER, M.D.,

Professor of Medicine at University College, London.

SINCE Mr. Tweedy first brought Duboisia myoropoides to the attention of the profession in England the alkaloid has been largely used as a topical application to the eye, in a solution corresponding to the officinal preparation of sulphate of atropia, namely, one grain in 120 minims. This application has caused many unpleasant symptoms. In one case under my care the duboisia caused much weakness, depression, and giddiness; he felt as if he were drunk. Another patient said it causes "great discomfort in my stomach, and a feeling as if a huge lump was in my throat. My power of distinguishing one article of food from another by the taste is taken away." In this patient it also caused great giddiness.

These accounts led me to test with the assistance of Mr. W. H. Neale the relative action of sulphate of atropia and sulphate of duboisia.

We first administered by the mouth a dose of sulphate of duboisia, and carefully noted the symptoms, and we then, on a subsequent day, gave a corresponding dose of sulphate of atropia.

On one occasion we gave two doses of $\frac{1}{120}$ grain of sulphate of atropia at an interval of two hours. On five occasions we gave $\frac{1}{120}$ grain.

Duboisia, we find, produces identically the same symptoms as atropia, but is far more powerful than atropia.

After duboisia, the symptoms begin in about half an hour, and reach their height in about two hours. The earliest symptom is dryness of the mouth.

After $\frac{1}{120}$ grain, there occurred great dryness of the mouth; dilatation of the pupils; much giddiness, almost preventing walking, and increased by exercise; slight drowsiness and rambling; great weakness, so that the limbs felt heavy and were raised obviously with considerable difficulty, with so much difficulty, indeed, that the woman could scarcely feed herself, and her grasp was very weak. It produced flushing of the face, and on one occasion patchy erythematous redness, the skin at these places being rather swollen and hard. The pulse became much fuller and rather slower. These symptoms lasted about seven to eight hours.

The same dose of sulphate of atropia only produced slight subjective dryness of the mouth.

After the administration of $\frac{1}{60}$ grain in two doses, with two hours interval, we observed the same symptoms for the most part. The man became very drowsy and delirious; his delirium was of the busy kind, he incessantly tried to pick up imaginary things from the floor. He had also decided twitchings of his limbs, and his pulse rose from 84 to 120, and his respirations from 18 to 30 per minute. The symptoms left him in about ten hours. The $\frac{1}{60}$ grain of atropia, on a subsequent day, only caused subjective dryness of his mouth.

These observations confirm my previous observations, published in the *Lancet* for 1878. I then found that duboisia, in addition to the symptoms above detailed, causes headache, checks perspiration, antagonizes the action of muscarin on the heart, and produces late tetanus in frogs—effects it possesses in common with atropia.

Duboisia, then, possesses the same properties as atropia, but is far more powerful than atropia. Mr. Tweedy found this to be the case in regard to the local application to the eye. But whilst duboisia is far more powerful than atropia on man, the reverse is the case in respect to frogs.

I injected hypodermically $\frac{1}{5}$ grain of sulphate of duboisia under the skin of a frog weighing 21 grammes. In 25 minutes the frog was a little weak; this weakness progressed, bu

was always far from complete, and disappeared entirely in five hours. Throughout the experiment the heart beat well at 48.

The same dose of sulphate of atropia given to a frog weighing 19 grammes caused complete paralysis in 25 minutes, persisting more than eight hours. The heart fell to 24 per minute, and became very weak, and breathing was arrested.

In another frog, weighing 22 grammes, we gave $\frac{4}{25}$ grain of sulphate of duboisia. In an hour the frog was so weak it could only just crawl. It recovered completely in three hours. The heart beat strongly throughout the experiment at 36 per minute, and the breathing never ceased.

We gave the same dose of sulphate of atropia to a frog of the same weight. In an hour the frog was completely paralysed, and nine hours afterwards the animal could not crawl. In 24 hours it had recovered, but was slightly tetanic. The heart fell to 20 and became weak, and the breathing ceased.

Atropia, therefore, paralyses far more powerfully the motor nervous system, the heart and respirations, in frogs than duboisia.

THE PRACTITIONER.

OCTOBER, 1880.

Original Communications.

ON THE PHYSIOLOGICAL ACTION OF AN ALKALOID EXTRACTED FROM THE GARDEN TULIP—NATURAL ORDER LILIACEÆ.

BY SYDNEY RINGER, M.D.,

Professor of Medicine at University College, London.

After investigating the physiological action of the daffodil, narcissus, snowdrop, and Hæmanthus, plants belonging to the natural order Amaryllidaceæ, I next turned to the study of the action of plants belonging to the closely allied order Liliaceæ.

Mr. Gerrard extracted for me an alkaloid from the bulbs, leaves, and flowers of the garden tulip, each pound of plant yielding a grain of nitrate of tulipine.

I first applied a 1 in 20 solution of the nitrate of tulipine to the eye of a cat, repeating the application frequently at a few minutes' interval. It produced some smarting, and very free salivation. The pupil remained unaffected.

Several days after this trial of the tulipine I applied a solution of nitrate of silver to the same eye to ascertain whether the salivation was due simply to irritation of the eye or to the topical action of the alkaloid on the mucous membrane of the mouth. Though the nitrate of silver irritated the eye far more than the tulipine solution, it produced very little salivation;

hence the alkaloid probably acted topically on the mucous membrane of the mouth.

On applying a little of the solution to his tongue Mr. Gerrard found that it caused tingling of that member, and of the throat—a tingling like that of aconite, lasting several hours.

I next tested the action of tulipine on frogs. I injected $\frac{3}{10}$ and $\frac{1}{5}$ grain of the nitrate respectively into two frogs, one weighing twenty-six and the other twenty-five grammes. In a few minutes the movements became stiff, suggesting the onset of tetanus. The stiffness increased, and the movements grew weaker; and then I noticed that the muscular contractions were peculiar. The muscle contracted slowly, and still more slowly relaxed; indeed the muscular movement exactly resembled that produced by veratria. Reflex action was soon lost, whilst some voluntary power still remained. On testing the muscles with the interrupted current, I found the contraction similar to that which occurred in a voluntary movement, the contraction being slow and the relaxation still slower. In about forty-five minutes the limbs became stiff on passive movement, whilst some voluntary movement remained and the muscles still contracted, both by direct electric stimulation, and by stimulation through their nerves. It seemed as if rigor mortis had set in before complete loss of muscular irritability. As the muscular contractility grew less, the stiffness of the muscles increased. In four hours all muscular irritability had ceased, notwithstanding the direct application to the exposed muscles of a strong interrupted current from a one-celled Daniels battery, with Du Bois Reymond's induction apparatus. At this time the muscles of an unpoisoned, brainless, test-frog contracted well; indeed sixteen hours after destruction of the brain the muscles contracted well with Du Bois Reymond's apparatus at fifteen centimetres' distance of the secondary from the primary coil.

Mr. North, Sharpey Scholar at University College, kindly took a tracing of the muscle-curve, and thus confirmed the phenomena previously described. It showed that the muscular contraction and relaxation are greatly prolonged, and at the same time weakened, so that at last the curve rises only just above the base line; yet the duration of the contraction, and

especially of the relaxation, is several times longer than in the tracing derived from an unpoisoned muscle.

From the early loss of muscular contractility, from the slow contraction and still slower relaxation of the muscle, and from the early onset of rigidity, it is evident that tulipine is a muscle poison.

We noticed that at a period when galvanic stimulation to the sciatic nerve caused the calf muscles to contract vigorously, all reflex action had ceased, showing that this alkaloid must paralyse either the afferent nerves or the reflex function of the cord. The small quantity of alkaloid at my disposal being now exhausted, I could not determine which of these structures the drug had affected. This alkaloid, as we have seen, affects not only the muscles like veratria, but like veratria also causes tingling, hence very possibly it is a poison to the afferent (sensory) nerves.

In frogs killed with tulipine I find the ventricle small, pale, and rigid, like the heart poisoned with veratria. Tulipine stops the ventricle sooner than the auricles.

Conclusions.

Tulipine differs almost entirely from the action of alkaloids derived from the plants belonging to the natural order Amaryllidaceæ so far as I have examined.

Tulipine is a muscle poison, affecting the muscles like veratria. It is, however, weaker than veratria.

It paralyses either the cord or the afferent nerves, or both; but probably it affects the afferent nerves.

Its action on the motor nerves if any, is but slight.

It affects the heart of frogs like veratria.

It does not affect the pupil.

On the Action of Extract of Muscaria, of Nitrate of Pilocarpine, and of Extract of Jaborandi on the Ventricle of the Frog's Heart, and on the Antagonising Action of Atropia.

By SYDNEY RINGER, M.D.

[From the *Practitioner*. Vol. xxvi., page 5.]

In vol. ii., page 241, of the *Journal of Physiology* I endeavoured to prove that muscaria and pilocarpine weaken and paralyse the heart by their action on the excito-motory apparatus and the muscular tissue, and not by stimulating the cardiac inhibitory apparatus; and that atropia antagonises these poisons by its action on the same structures, and not by paralysing the inhibitory apparatus.

I made these experiments on portions of the frog's heart placed in saline solution. When the extract of muscaria or pilocarpine solution had arrested contractility, both spontaneous and from mechanical stimulation, I applied the atropia solution, and speedily contractility returned. In this paper I have continued this investigation, using Roy's tonometer (as suggested to me by Dr. Foster), by which the heart is fed with blood and kept beating many hours, and the beats are easily recorded on a revolving cylinder; and these experiments fully confirm my previous conclusions. After destroying the brain and spinal cord I opened the thorax and made an incision into the sinus venosus, and divided the septum between the auricles, and then introduced the cannula, and fixed the heart by tying a ligature in the auriculo-ventricular groove. I thus experimented with the ventricle and a portion of

the groove, this part of the heart not containing any of the inhibitory apparatus. I used one part of sheep's or bullock's blood diluted with two parts of saline solution. I first took tracings with the unpoisoned blood, then with the blood poisoned with extract of muscaria or jaborandi, and then with the same blood with some atropia added to it. These experiments were made in March and April, and the frogs were kept in the cellars of the College.

I shall first speak of the action of extract of muscaria.

In a recent paper[1] W. H. Gaskell records an experiment with Roy's tonometer, showing the paralysing action of muscaria on the apex of the ventricle of the frog's heart, and he concludes that muscaria affects the muscular substance of the heart as lactic acid does; that both "gradually lower the height of each contraction in the case of the beating ventricle, and the tracing of each shows the pointed apex, characteristic of the action of the lactic acid solution." Gaskell also concludes from his experiments "that muscaria produces its effects upon the heart by its action upon the muscular tissue, rather than by the excitation of any inhibitory apparatus."

As Roy points out, the action of the unpoisoned ventricle differs in different hearts, and I find that this difference modifies the action of the poison. With some ventricles there occurs a series of contractions, followed by a pause, but with others no pauses occur, but the contractions are quite uniform, both as regards strength and frequency. With a heart in which pauses occur the extract of muscaria greatly prolongs the pause, so that a heart whose pauses last only for a few seconds after the application of extract of muscaria, stops for five minutes or even longer. The number of beats after the pause also grow less and less, till at last each pause is followed by only one beat. In other respects the influence of the extract is the same as in those cases where no pauses occur.

Where the heart beats uniformly, the extract of muscaria at first accelerates the beats, whilst weakening each beat,

---

[1] "Tonicity of the Heart," *Journal of Physiology*, vol. iii., p. 59.

but after a time the number of beats becomes less frequent than before the poisoning. The muscaria modifies the character of each beat, lessening its amplitude as well as its duration, so that the apex of the trace becomes pointed. My experiments, therefore, confirm Gaskell's observations in all particulars.

If a large dose be added to the circulating fluid, the ventricle is speedily arrested, the trace becoming smaller, sharper at its point, and shorter in duration, till the ventricle stops after a few beats. In a few seconds, however, the contractions return, weak at first. The height and breadth of the trace gradually increase, but the trace never becomes so good as before the poisoning by extract of muscaria. If a very large dose of extract of muscaria is employed, the heart very speedily becomes permanently arrested. In all my experiments, on the addition of a little sulphate of atropia, the contractions returned. The effect of extract of muscaria and the antagonising action of atropia are well seen in the accompanying figures.

My solution of extract of muscaria had a decided acid reaction, and it occurred to me as possible that the paralysis of the ventricle might be due to the acidity, for very weak acid solutions at once arrest ciliary motion. I made the following experiments to decide this question: After arresting the heart with extract of muscaria, I added to the circulating blood some solution containing a small quantity of caustic soda, but without restoring the contraction. I then added ten minims of a 2 per cent. solution of atropia, and the pulsations speedily returned. I next added sufficient solution of caustic soda to render the extract of muscaria slightly alkaline. Some of this I used with Roy's method, and it arrested the heart, whilst atropia restored the contractions.

I also exposed the heart of a brainless frog and applied some of this alkaline solution of muscaria. It at once slowed and soon stopped the action of the heart, and a small quantity of an atropia solution speedily restored the contractions.

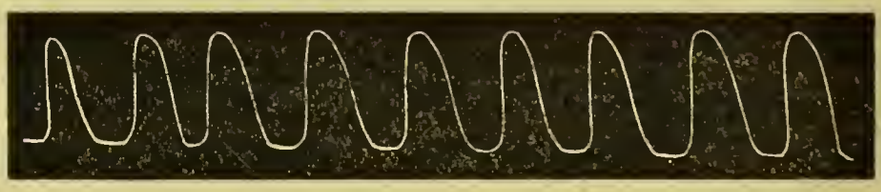
These experiments show that the paralysis of the ventricle is not due to the acidity of the solution.

These observations prove that extract of muscaria paralyses the ventricle, separated from the auricles, and as this contains no inhibitory ganglia, extract of muscaria does not arrest the ventricle by stimulating the inhibitory apparatus, but by paralysing either the excito-motory ganglia, or the muscular substance, or both these structures. These observations further show that atropia antagonises the action of extract of muscaria on the excito-motory ganglia, or the muscular substance.

DESCRIPTION OF TRACINGS.

Experiment I.

Trace I.—Before the addition of Extract of Muscaria.



Trace II.—After the addition of Extract of Muscaria.

Trace III.—Half an hour after the addition of Sulphate of Atropia.

EXPERIMENT II.

TRACE IV.—Before the addition of Extract of Muscaria, which quickly arrested the ventricle.

TRACE V.—Twenty-six minutes after the addition of Sulphate of Atropia.

EXPERIMENT III.

TRACE VI.—Before the addition of Extract of Muscaria.

TRACE VII.—Eighty minutes after the addition of Muscaria.

TRACE VIII.—Fifteen minutes after the addition of Atropia.

I next experimented with pilocarpine and extract of jaborandi. I find that pilocarpine only slightly affects the ventricle, although in one of the experiments a grain of the

nitrate was added to the circulating fluid, and this passed many times through the ventricle. Pilocarpine at first slightly accelerates the beats, and then slows them. The character of the trace is slightly altered, its apex becoming sharper and its breadth less; thus pilocarpine, though possessing but a weak action on the ventricle, affects it in the same way as Gaskell finds lactic acid and muscaria affect the apex of the ventricle.

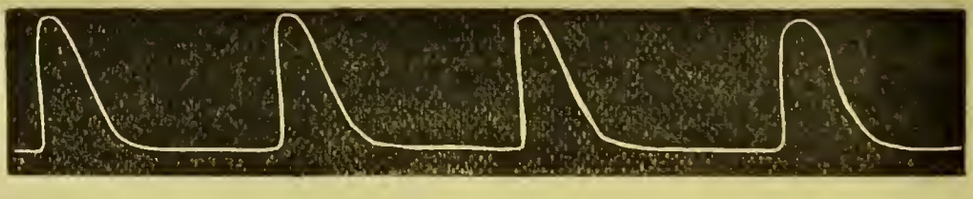
I have elsewhere shown that pilocarpine has only a very feeble action on the frog's heart *in situ*.

I then experimented with liquid extract of jaborandi, free from spirit.

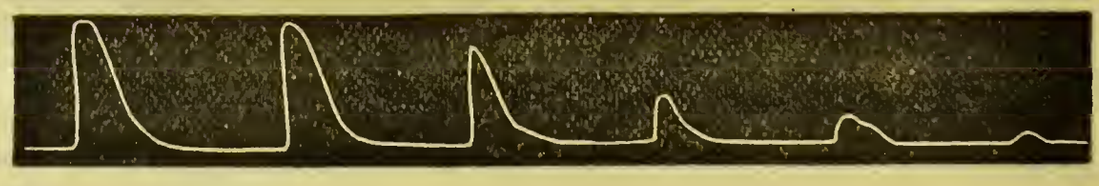
Extract of jaborandi is a powerful paralyser of the ventricle. In these, as in my former experiments, I used six ounces of blood and saline solution, and I find that ten minims of the liquid extract added to this fluid rapidly slows, and weakens the heart, whilst twenty minims stops the ventricle in about ten minutes, and thirty minims stopped the ventricle in a few seconds.

In all my experiments atropia antagonised the action of jaborandi, and restored good contractions to the ventricle.

The accompanying tracings, IX., X. and XI., show the effects of jaborandi and the antagonising action of atropia:



TRACE IX.—Before the addition of Jaborandi.

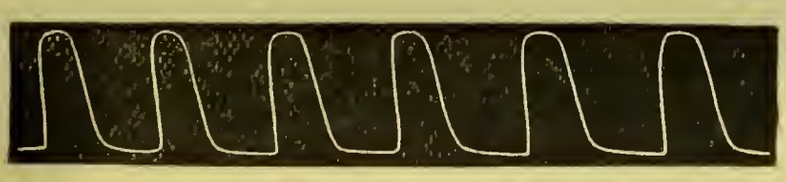


TRACE X.—Showing the effect of a large dose of Extract of Jaborandi.

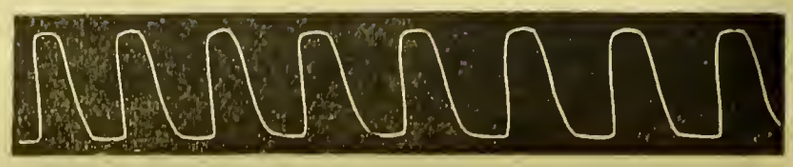
TRACE XI.—After the addition of Atropia.

It is obvious from the preceding experiments that pilocarpine is not the chief ingredient in jaborandi which depresses the heart, for a grain of pilocarpine only slightly weakened and slowed the ventricle. On the other hand, twenty minims of the liquid extract, freed from spirit, stopped the heart in ten minutes, whilst thirty minims of the extract stopped the ventricle after seven beats. Now, as the liquid extract yields about 3·4 per cent. of alkaloid, it is obvious that the liquid extract contains some substance which weakens and slows the ventricular action besides pilocarpine.

I determined to try and ascertain the nature of the powerful cardiac depressor, and Mr. Gerrard prepared for me a specimen of liquid extract without its alkaloid pilocarpine. He treated the liquid extract with ammonia and chloroform, which removed the pilocarpine and a resin. He gave me the residue, which I tested on the ventricle as in the previous experiments. I employed fifty minims of this liquid extract without alkaloid, which quickened the contractions from eighteen to twenty-six and rendered them rather weaker, but produced a far less powerful effect than a much smaller dose of the liquid extract, untreated by ammonia and chloroform.



TRACE XII.—Before the addition of Extract of Jaborandi, treated with Ammonia and Chloroform.



TRACE XIII.—After the addition of Extract of Jaborandi without alkaloid.

It is obvious, then, that the cardiac paralyser is not present, or at least only in a very slight degree, in the residue of the liquid extract after treatment by ammonia and chloroform.

Extract of jaborandi has a strong acid reaction, and I next made a few observations to ascertain if the acid of the extract causes the cardiac depression. If so, then it is probably not due simply to its acidity, but must be due to some specific action of the organic acid, for if due simply to acidity, then nitrate of pilocarpine, which gives a strong acid reaction, should have a more powerful action on the heart.

I made some of the liquid extract (freed from alcohol) slightly alkaline by the addition of a solution of soda hydrate. Ninety minims of this extract are required to arrest the ventricle, hence it is evident that the acid solution is a far more powerful paralyser of the heart than the alkaline solution. I find, however, that if the ventricle is stopped by the acid liquid extract the subsequent addition of soda hydrate to the blood will not restore the pulsations, whilst the addition of a small quantity of atropia at once made the ventricle beat well. But whilst the acid extract affects the detached ventricle, on Roy's apparatus, strange to say, the alkaline extract is the more powerful in arresting the entire heart *in situ*.

In all the experiments with the alkaline and acid solution of extract of jaborandi, atropia speedily antagonised the jaborandi, strengthening a weak heart and restoring good contractions to an arrested heart.

These experiments show that jaborandi and pilocarpine affect the ventricle separated from the auricles, and, as the ventricle contains no inhibitory ganglia, these substances

cannot affect the ventricle by inhibition, but must weaken or paralyse it by their effect on the excito-motory ganglia, or the muscular tissue, or both. As a heart arrested by jaborandi will at first contract on mechanical stimulation, but soon ceases to contract either on mechanical or electric stimulation, jaborandi, according to the current view, must paralyse both the excito-motory ganglia and the muscular substance of the ventricle. As atropia antagonises the action of jaborandi on the ventricle it cannot act by paralysing the inhibitory apparatus, but from its effects in the excito-motory ganglia and muscular substance, and I have elsewhere suggested that this antagonism is due to chemical displacement. The suggestion is as follows: pilocarpine (and muscaria) paralyses the heart by combining with the molecules of the excito-motory nervous apparatus, and of the muscular tissue of the heart. Atropia antagonises pilocarpine and muscaria because it has a stronger affinity for the muscular and nervous structure of the heart than these substances, and displaces them, replacing their effect by its own.

Influence of Anæsthetics on the Frog's Heart.

By SIDNEY RINGER, M.D.

[From the *Practitioner*. Vol. xxvi., page 436.]

Clinical experience has abundantly shown that chloroform is a far more dangerous anæsthetic than ether. The Medico-Chirurgical Society's[1] Committee shows that the chief difference in the relative power of these two agents is that chloroform arrests the heart's action much more readily than ether.

Professor Schäfer and Professor Fraser[2] have independently proved that chloroform acts by stimulating the vagus, and they counsel the employment of a small dose of atropia before the administration of chloroform.

The Committee of the British Medical Association[3] found that both chloroform and ethidene decidedly reduce blood-pressure, but ether produces no decided effect on blood-pressure. Chloroform, they found, reduces the pressure in a much greater degree than ethidene.

In this paper I record the results of experiments made in March, April, and May, regarding the effect of the anæsthetics chloroform, ethidene dichloride, ether, and bromide of ethyl, on the ventricle of the frog's heart.

I employed Roy's method. I attached the ventricle of the heart to the cannula by tying a ligature round the groove between the auricles and ventricle. The portion of the heart (ventricle, with a little of the groove) I used is free from inhibitory nerves or ganglia. The effect of the

[1] *Medico-Chirurgical Transactions*, vol. xlviii., p. 326.
[2] *British Medical Journal*, 1880.
[3] *British Medical Journal*, December 18, 1880.

anæsthetic, therefore, cannot be due to its influence on the inhibitory apparatus. I used dried blood.[1] This blood I dissolved in distilled water, and then diluted this solution with a saline solution—one part of blood being diluted with two of saline. This dissolved dried blood I found as efficacious as fresh blood. In each experiment I used three ounces of the blood-mixture, employing throughout each experiment the same blood, so that both the poison and its antidote were intermixed in it.

The tracings in this paper run from left to right.

These experiments are, I venture to think, important, since they demonstrate that chloroform and ethidene dichloride have each a powerful paralysing effect on the muscular substance of the ventricle, and arrest the heart's action, whilst ether, in much larger doses, greatly accelerates the frequency, and weakens but slightly the contractions, and since the heart beats with increased frequency, and so performs more work, this more than compensates for any slight diminution in the contraction of each pulsation. These experiments are practically important too, since they show that the application of ammonia will restore a heart arrested, or almost arrested, by chloroform, ethidene dichloride, or iodoform.

Action of Chloroform on the Heart.

Chloroform is a strong poison to the ventricle of the frog's heart. Just like lactic acid,[2] muscarin and jaborandi,[3] chloroform lessens both the height and duration of the trace till the heart stops in diastole. Trace I. well illustrates the effect of chloroform. In this experiment rather more than one minim of chloroform nearly stopped the ventricle, and when the contraction became scarcely perceptible, on adding to the blood ten minims of a 1 per cent. solution of strong liquor ammoniæ, the contractions

---

[1] Desiccated defibrinated bullock's blood, prepared by Parke, Davis and Co., Detroit, United States.

[2] Gaskell, *Journal of Physiology*, vol. iii., No. 1.

[3] *Practitioner*, January, 1881.

instantly became strengthened; and on adding another ten minims the ventricle improved still more, until the contractions became nearly as strong as before the experiment. I then added ten drops of pure chloroform to the blood and the heart stopped speedily.

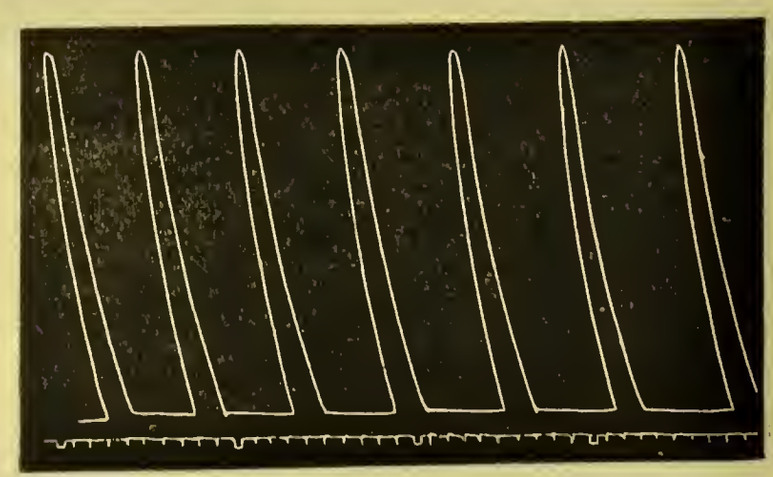
This experiment, then, clearly shows the powerful paralysing effect of chloroform, and that ammonia antagonises it, even to the extent of restoring completely an almost arrested heart; and further, that a larger dose of chloroform will counteract the effect of a moderate dose of ammonia.

The chloroform does not arrest the ventricle by stimulating the inhibitory apparatus; for the portion of the heart engaged contains no inhibitory nerves nor ganglia. The chloroform evidently paralyses the heart's muscular substance, for it is well known that the cardiac muscular tissue will beat rhythmically without the presence of nervous ganglia. It is evident, therefore, that, did the chloroform paralyse only the ganglia of the ventricle, the ventricle itself would still have continued to beat. Some further experiments I made with the lower half only of the ventricle render this reference certain. Chloroform, I found, affects the ganglionless and nerveless portion in exactly the same way as the whole ventricle.

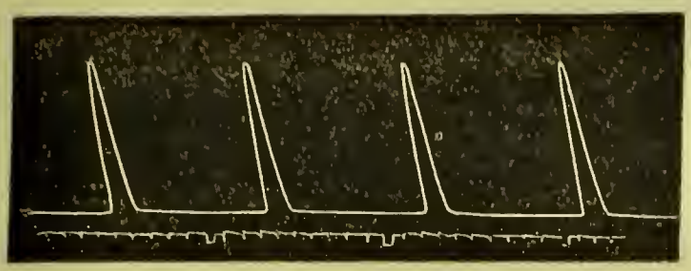
March 27, 1881.

TRACE I.

Before the addition of chloroform :



Six minutes after the addition of sixty minims of $\frac{1}{2}$ per cent. solution of chloroform in water:

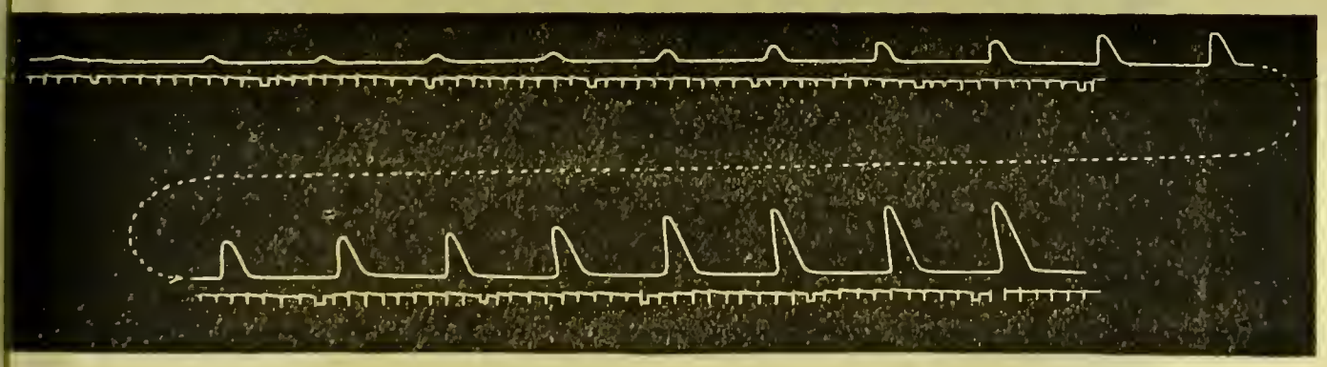


Six minutes after an additional sixty minims:

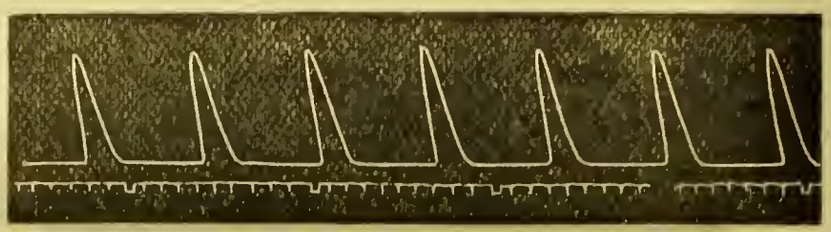
Three minutes after an additional dose of 120 minims, in all $1\frac{1}{5}$ minims of chloroform:

I then added ten minims of a 1 per cent. solution of ammonia, and immediately produced the following result:

Ammonia added.

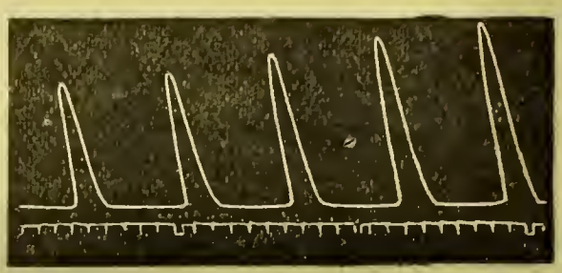


Five and a half minutes after the addition of ammonia :

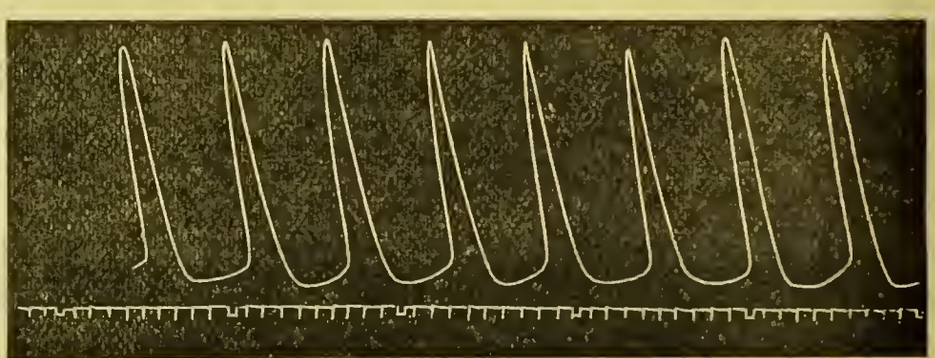


I next added another ten minims of the ammonia solution, and immediately the trace improved :

Ammonia added→

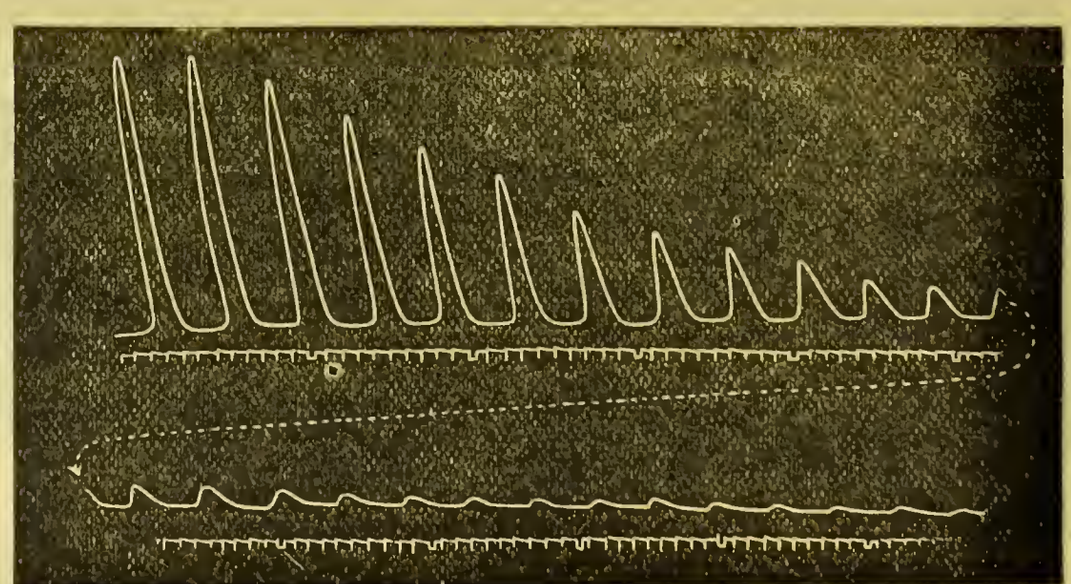


One minute after the addition of the last dose of ammonia :



I then added ten drops of pure chloroform with the following effect :

Chloroform added.



Thirty drops of the 1 per cent. ammonia solution raised the trace high above the base line, but did not restore the pulsation :

As might be expected, a heart weakened with chloroform will sometimes slowly recover spontaneously, owing, probably, to the evaporation of the drug, but when under chloroform a heart is greatly weakened almost to the point of arrest, it rarely recovers ; and if so, the recovery is very gradual, and never so rapid as after a dose of ammonia to the blood. In fact, the improvement is not due to evaporation of the chloroform, but is obviously caused by the ammonia antidoting the chloroform.

I find that atropia does not antagonise the action of chloroform on the ventricle. I added successive doses of chloroform to the circulating blood, in all 0·65 minims. This greatly weakened, but did not arrest, the heart. I then added successive doses, in all 0·4 grains, of sulphate atropia, but the heart grew rapidly weaker and soon stopped.

On another occasion I added atropia first and then chloroform, to see if atropia could prevent the action of chloroform. I added first five and then ten minims of a 1 per cent. solution of sulphate of atropia. These produced little or no effect on the trace. I then added thirty, forty, thirty minims of a 0·5 per cent. solution of chloroform ; the contractions rapidly grew weaker and weaker till they well-nigh stopped.

ETHIDENE DICHLORIDE.

Ethidene dichloride affects the ventricle just like chloroform, and I think in an equal degree. A minim and a half

added to the three ounces of blood-mixture soon makes the trace sharper at its apex, and then it rises less, and the systole continues a shorter time. In about twenty-five to thirty minutes the contractions become less frequent and very small. Ten minims of a 1 per cent. solution of ammonia greatly strengthens and accelerates the beats; and the addition of another ten minims of ammonia solution restores the beats nearly to their original character. Another addition of ten minims of ammonia solution then changes the trace altogether; changes it, in fact, to the shape produced by the ammonia itself.

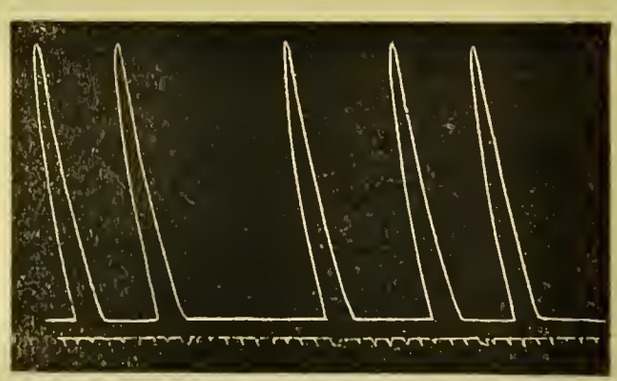
As the effects of ethidene dichloride are in all respects like those of chloroform, it is not necessary to give tracings of the ventricular contractions.

ANHYDROUS ETHYLIC ETHER.

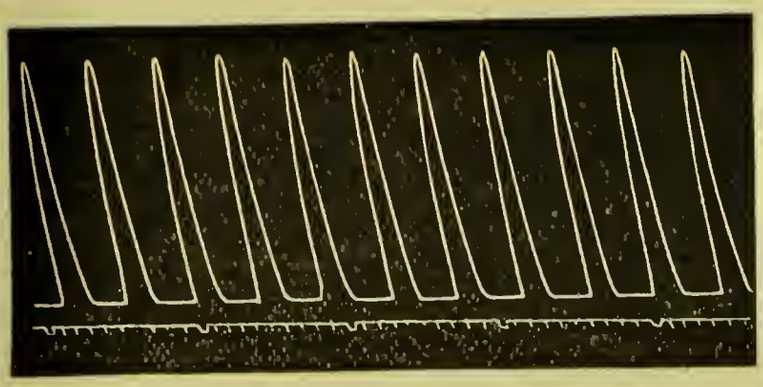
Ether affects the heart in far less degree than either chloroform or ethidene dichloride, as the following traces show :—

Trace II.

Before ether :

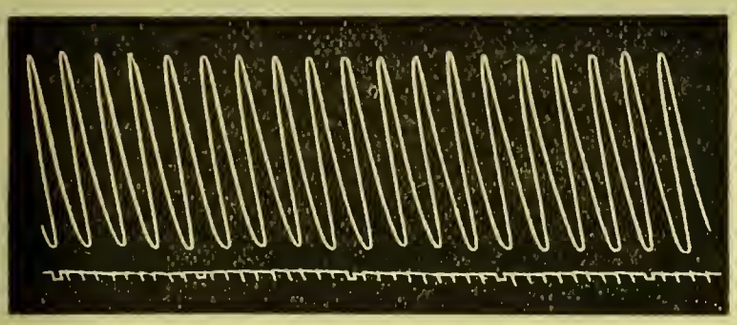


I then added $\frac{1}{5}$, $\frac{1}{5}$, $\frac{1}{5}$, $\frac{3}{5}$ and one minim of ether ($\frac{1}{2}$ per cent. watery solution) in successive doses, two minims in all, without producing any effect on the trace. I then added five minims, which produced the following trace, taken twenty-five minutes after the first dose and four minutes after the last :



Seven minims of ethylic ether, therefore, accelerated the beats, and each beat became a little weaker, which generally occurs when the heart beats more frequently.

I then added another five minims, twelve in all. The following trace was taken twenty-eight minutes after the first dose and three minutes and a half after the last dose :



This large dose of twelve minims greatly accelerated the beats, and made each beat a little weaker, but the amount of work done by the heart must have been greater than before the addition of ether, the increased frequency more than compensating for the diminished force of each contraction.

In another experiment two, five, and five minims successively of anhydrous ether greatly accelerated and rather strengthened the contractions.

In another experiment I added separately five, ten, fifteen and twenty minims of anhydrous ether to the circulating blood, and greatly accelerated the beats, whilst slightly weakening them.

On another occasion (see Trace III.) I added fifty minims

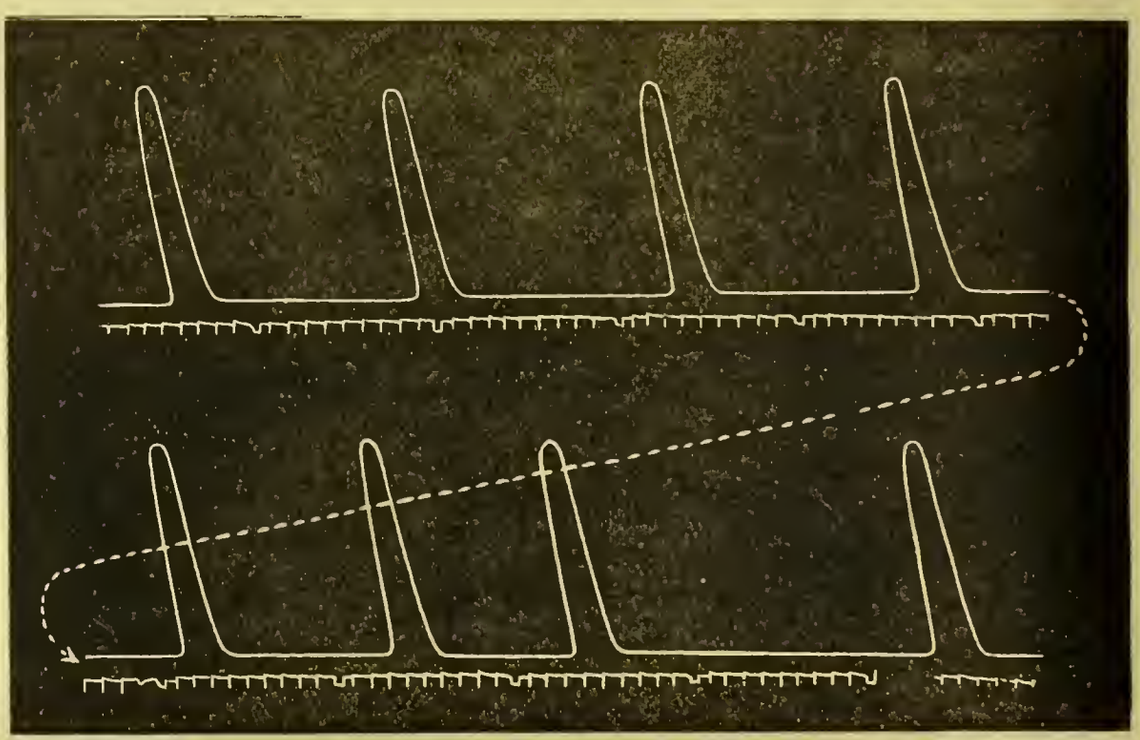
of anhydrous ether and slightly accelerated and weakened the contractions. An additional fifty minims speedily arrested the heart in diastole.

Ether, therefore, induces very little paralysing effect on the ventricle. In fifty-minim doses it accelerates and somewhat weakens its action, but from the great acceleration the ventricle must perform more work than before the addition of ether.

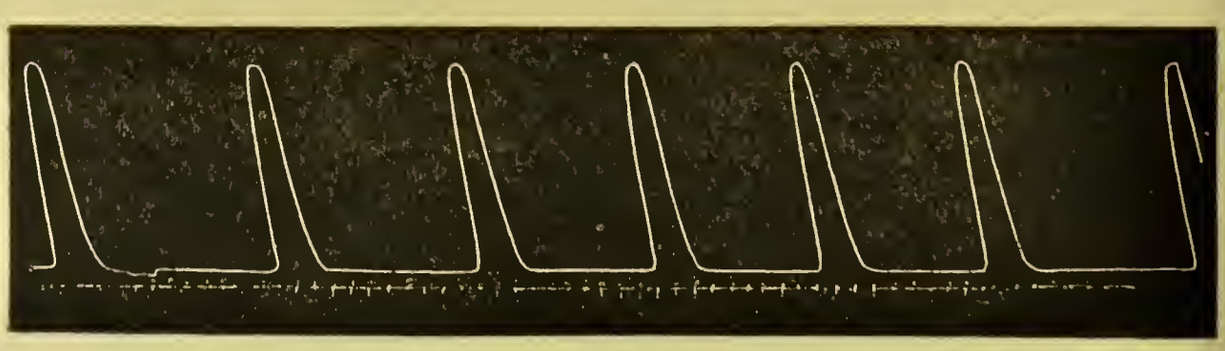
Ammonia and ether, like chloroform and ammonia, are mutually antagonistic as regards the whole ventricle. I have not tested their action on the apex only of the ventricle.

TRACE III.

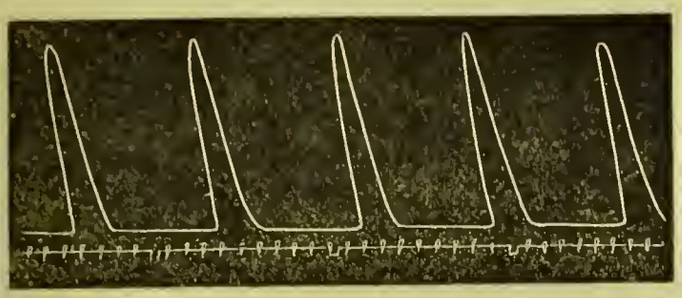
Before ether :



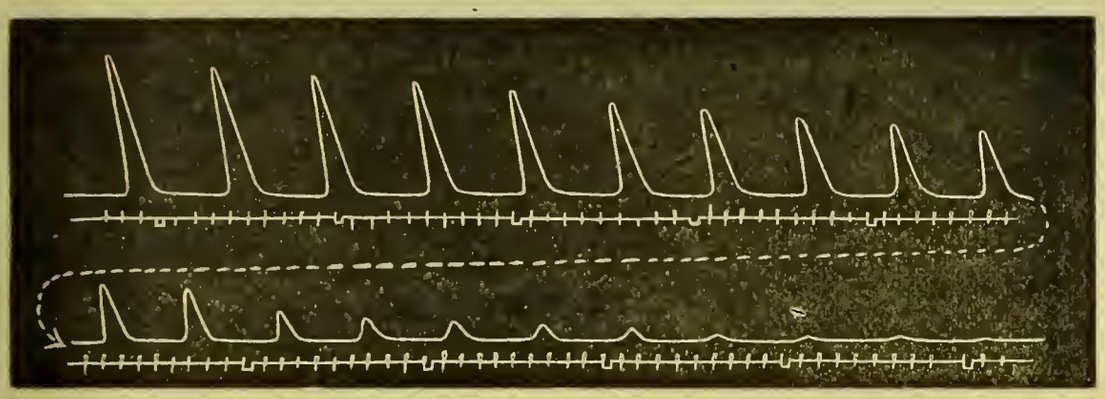
Ten minutes after twenty minims of anhydrous ethylic ether :



Then I added thirty minims and produced the following traces fifteen minutes after the first dose, five minutes after the second :



Then I added fifty minims of ether. The following trace was taken seventeen minutes after the first dose, two minutes after the last dose :



I then added, in successive doses, ten, ten, ten, and twenty minims of the solution of ammonia, which failed to restore the contractions, and only raised the trace higher above the abscissa :

In several experiments, after finding that ether produced so little effect on the ventricle, I added one minim of chloroform, which rapidly weakened and arrested the heart ; and then I added a solution of ammonia and restored the contraction ; but I found that large doses of ammonia were required to antagonise the chloroform.

The difference, therefore, between the action on the ven-

tricle of chloroform or ethidene dichloride on the one hand, and ether on the other, is most marked ; for whilst one to two minims of chloroform or ethidene dichloride rapidly weakens and arrests the ventricle, even fifty minims of anhydrous ether merely accelerates the beats and weakens them a little, yet the total amount of work done is increased, for the increased frequency more than compensates, I think, for the slightly diminished force of the contraction.

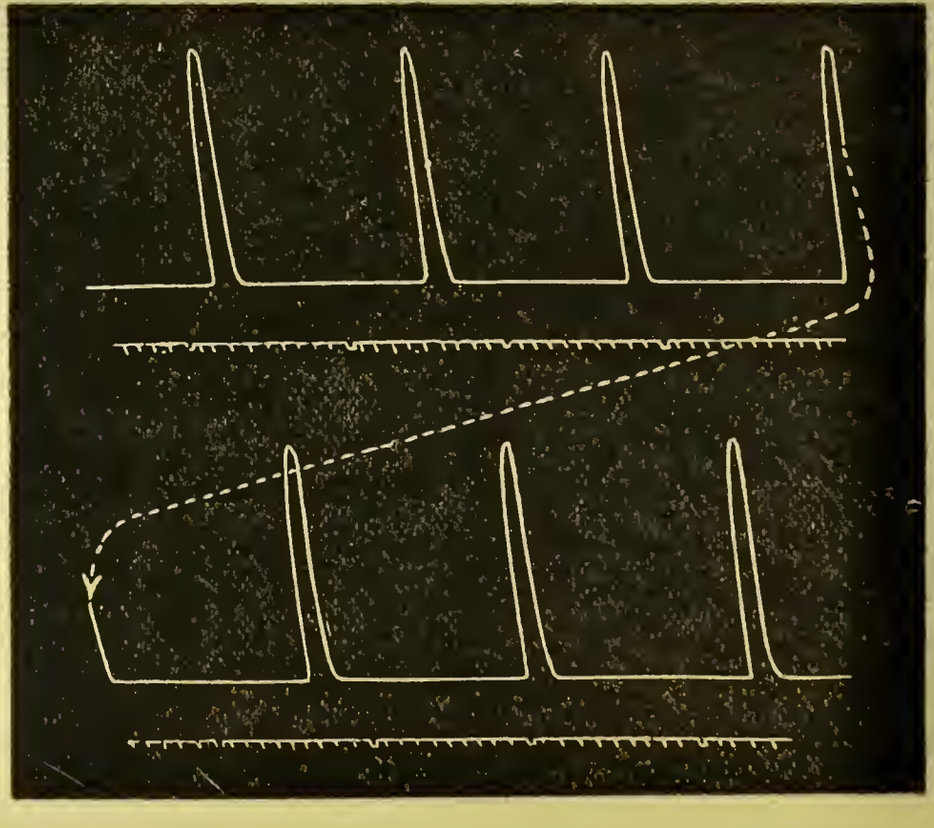
It must be borne in mind that chloroform is heavier than ether and less volatile, so that ether would evaporate from the blood quicker than chloroform ; but I took precautions to lessen evaporation to a considerable extent.

BROMIDE OF ETHYL.

Bromide of ethyl arrests the ventricle, and must therefore act on the muscular substance of the heart. It is far less powerful than chloroform, but more poisonous than ether. Thus in one experiment twenty minims, and in another fifty-five minims, arrested the ventricular contractions. Like ether, bromide of ethyl accelerates the beats.

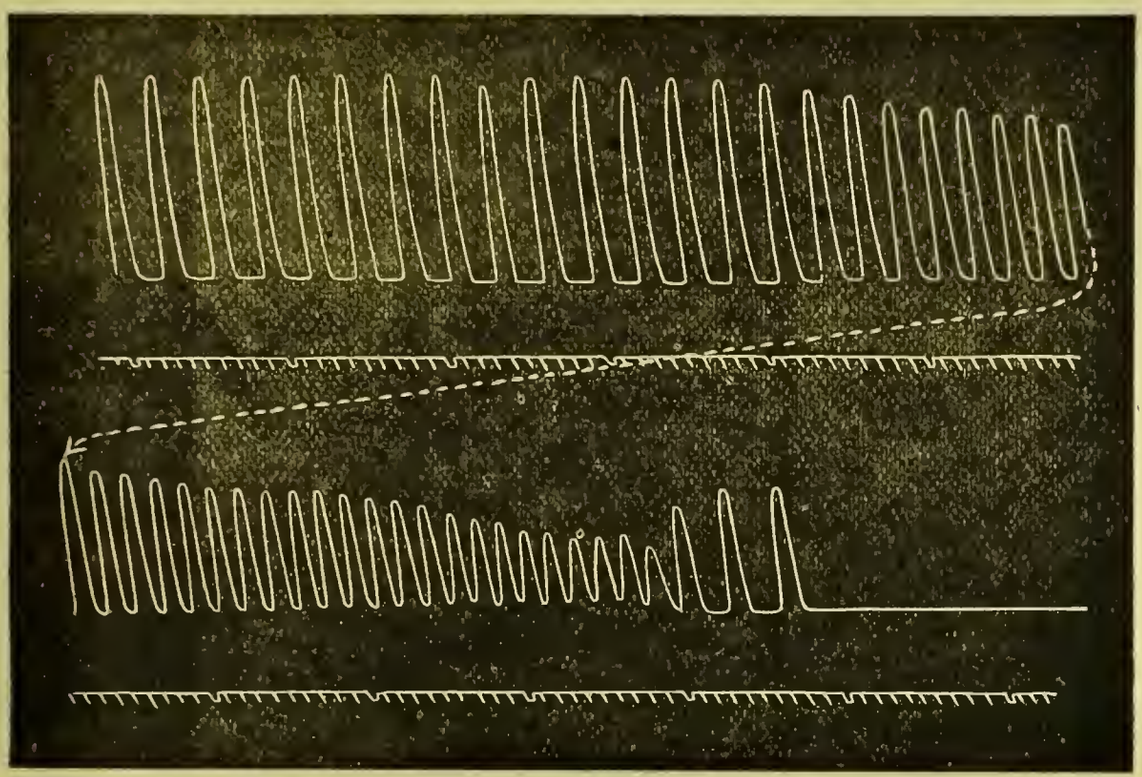
TRACE IV.

Before the addition of bromide of ethyl :

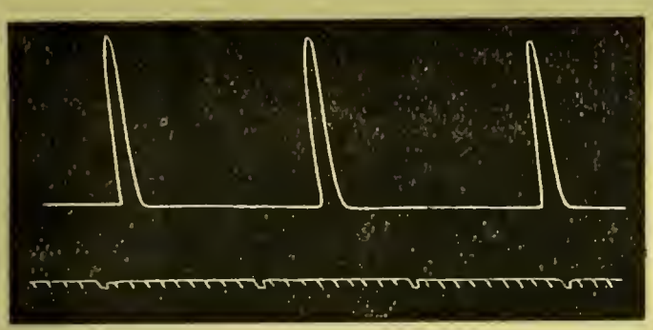


Seven minutes after the addition of ten minims of bromide of ethyl: (This trace also shows the effect of a second dose of ten minims :)

2nd ten minims.



The heart then stopped, but on galvanic stimulation it gave the following contractions—one after each stimulation :



Twelve minutes after the last dose galvanic stimulation caused scarcely any contraction :

In another experiment $\frac{1}{5}$ minim and $\frac{1}{2}$ minim accelerated the heart's action and rather weakened it, but the heart was not arrested till fifty-five minims in successive doses were added to the blood. With these large doses the heart grew weaker and weaker and less frequent, till the frequency became about the same as before the ventricle was poisoned. At last the ventricle stopped.

Chloroform and ammonia are mutually antagonistic in respect of their action on the whole ventricle, and also on the apex of the ventricle; and I venture to hope that these experiments, will settle this much-vexed question, and show that some drugs at all events are mutually antagonistic.

Rossbach[1] contends that drugs are not mutually antagonistic. He maintains that when a tissue is paralysed by one poison it cannot be stimulated by another poison. For instance, he maintains that whilst atropia antagonises pilocarpine, pilocarpine cannot antagonise atropia — that atropia paralyses the sweat apparatus, and pilocarpine no longer is able to stimulate it again into action. He admits that after small doses of atropia pilocarpine can produce sweating, and he explains this action by assuming that atropia paralyses the nerve of the sweat gland, and later the gland apparatus. After a small dose of atropia the nerve only is paralysed, and then pilocarpine can still stimulate the glandular cells; but a large dose of atropia paralyses the glandular cells also, and then pilocarpine is debarred from forming a secretion of sweat.

Langley[2] has, I think successfully, controverted these hypotheses, and shown the fallacy of Rossbach's experiments. In my experiments with the lower half of the ventricle there is one structure only involved, namely, muscular tissue, so that if two drugs mutually antagonise each other, it cannot be by their action on different structures. Now, I find chloroform and ammonia are mutually antagonistic as regards their action on the apex of the ventricle.

---

[1] Pfluger's *Archiv.*, Bd. xxi., Hf. 1, p. 1. 1879.

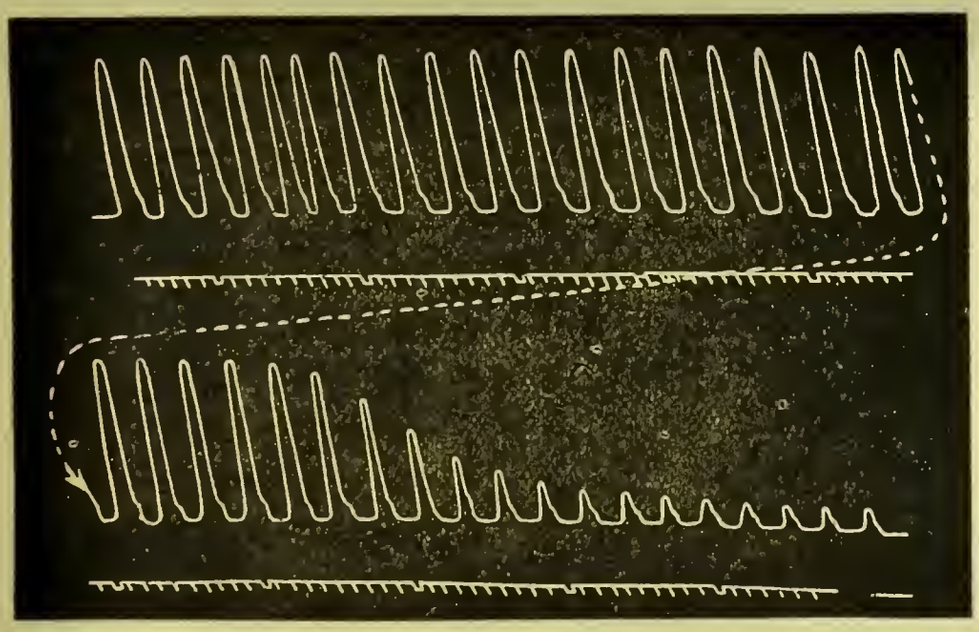
[2] *Journal of Physiology*, vol. iii., No. 1.

The cardiac contractions greatly weakened by chloroform are strengthened by ammonia, and are again weakened by a further addition of chloroform, and again strengthened by another addition of ammonia; at last a dose is reached which destroys the rhythmical contractions, yet still in this process a mutual antagonism is displayed. Ammonia, like soda and digitalis, lessens the diastolic dilatation of the ventricle, and at last arrests it in strong systole. Chloroform, as these traces show, arrests the heart in diastole. After a large dose of chloroform and ammonia alternately given is reached, the rhythmic contractions cease; but on the addition of ammonia, the heart passes from diastole into strong systole, and on the addition of chloroform the heart again becomes dilated, to be again contracted on the addition of ammonia. At last the heart remains in a midway state—neither in strong systole nor diastole.

Iodoform and ammonia are also mutually antagonistic, as the following trace with the whole ventricle shows:—

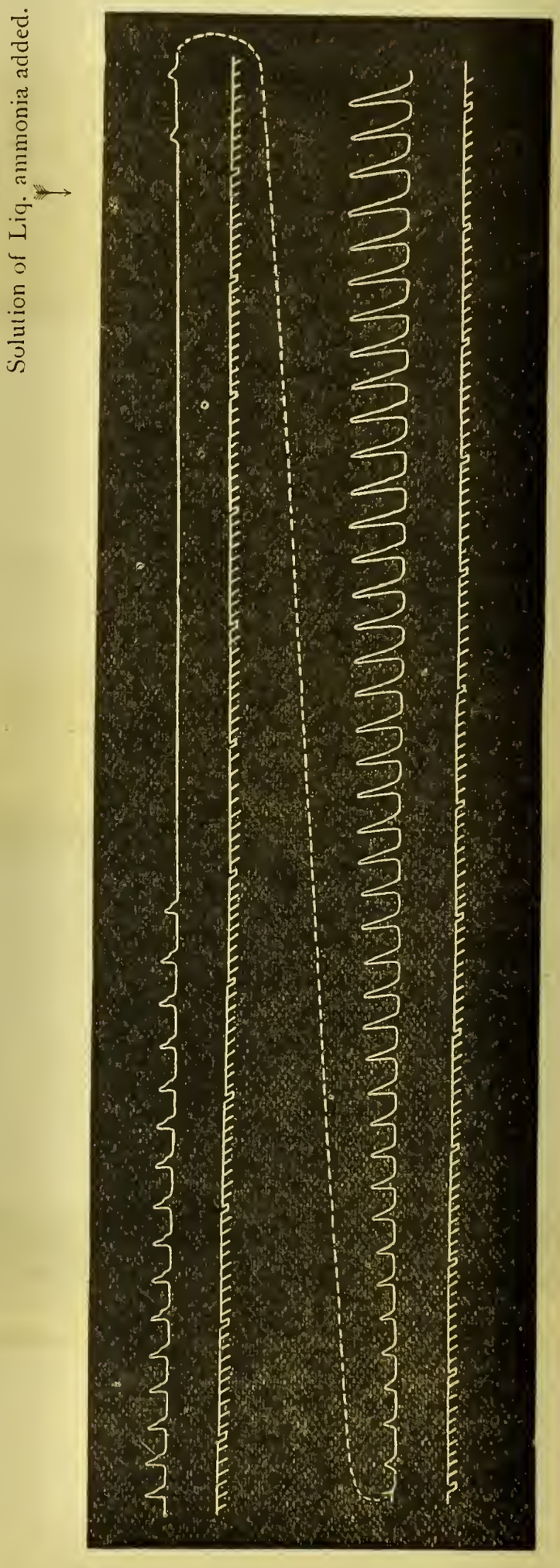
Trace before and after the addition of twenty minims of a 1 per cent. solution of iodoform in rectified spirits:

Iodoform added.

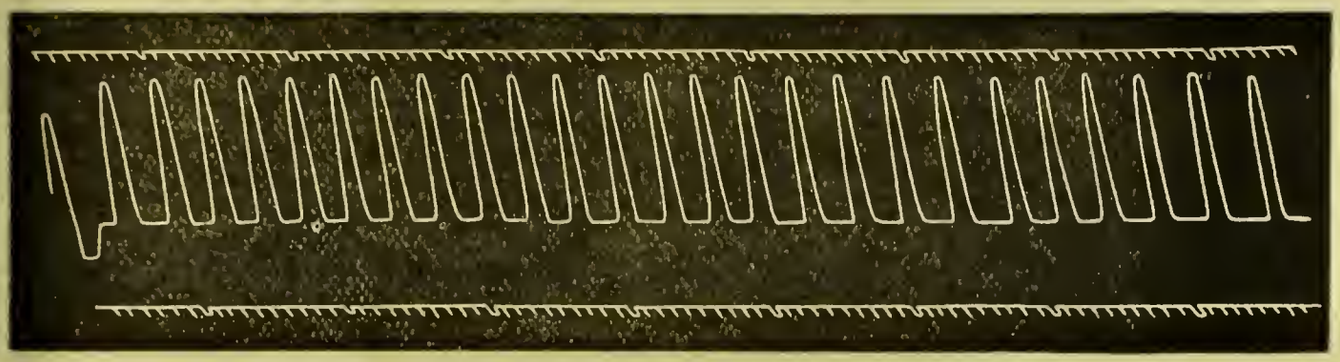


The trace continued the same for about three minutes, and then stopped. On adding ten minims of 1 per cent.

solution of ammonia the ventricular contractions returned, as shown in the following trace:

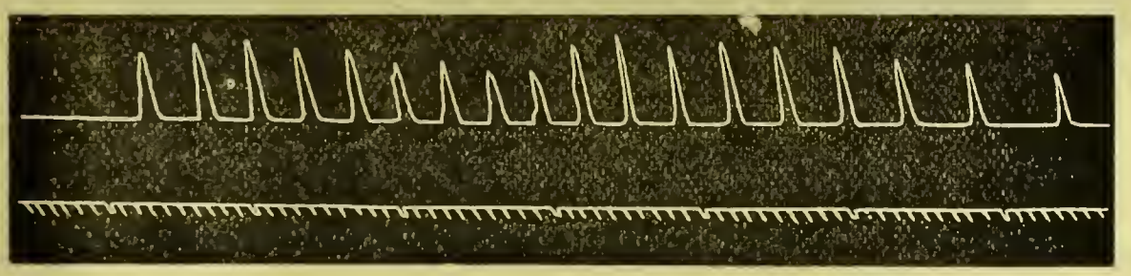


Twenty minutes after the addition of ammonia the heart gave the following trace :



Then I added ten minims of the iodoform solution. This weakened only the contractions, and I added another ten minims to the blood, with the following effect :

Iodoform added.



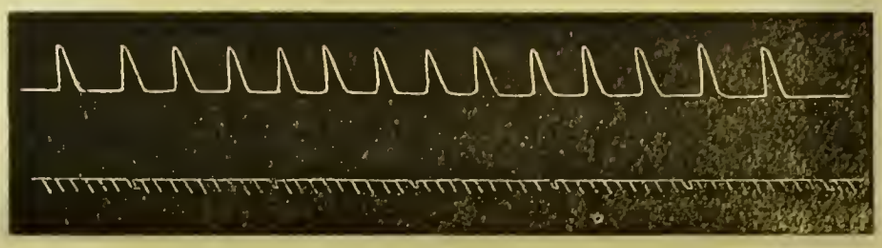
Then I added ten minims of the ammonia solution, but this produced very little effect, and I added another ten minims.

Trace just before and after the last dose of ammonia :

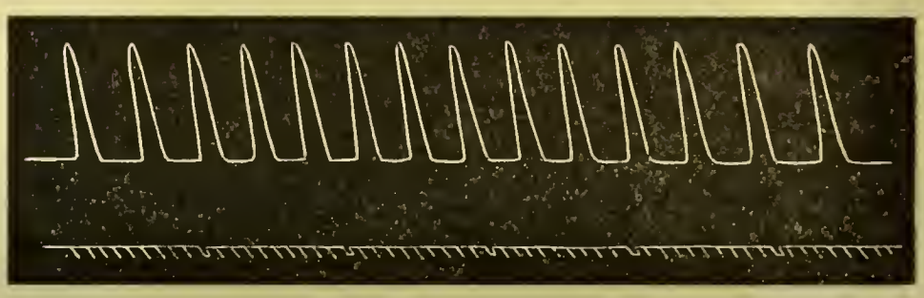
Ammonia added.

In six minutes later the heart gave the following trace, when I added another ten minims of ammonia :

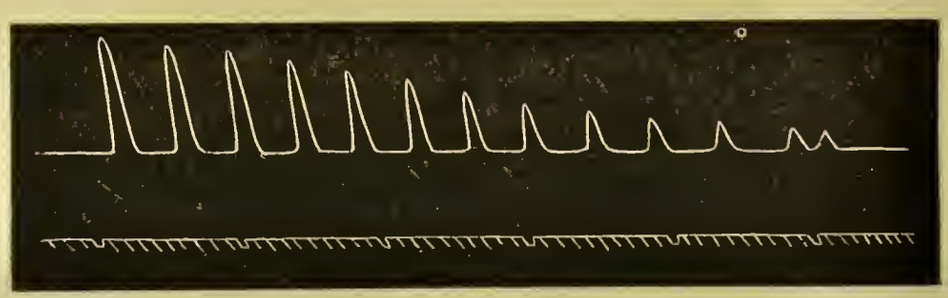
Ammonia added.



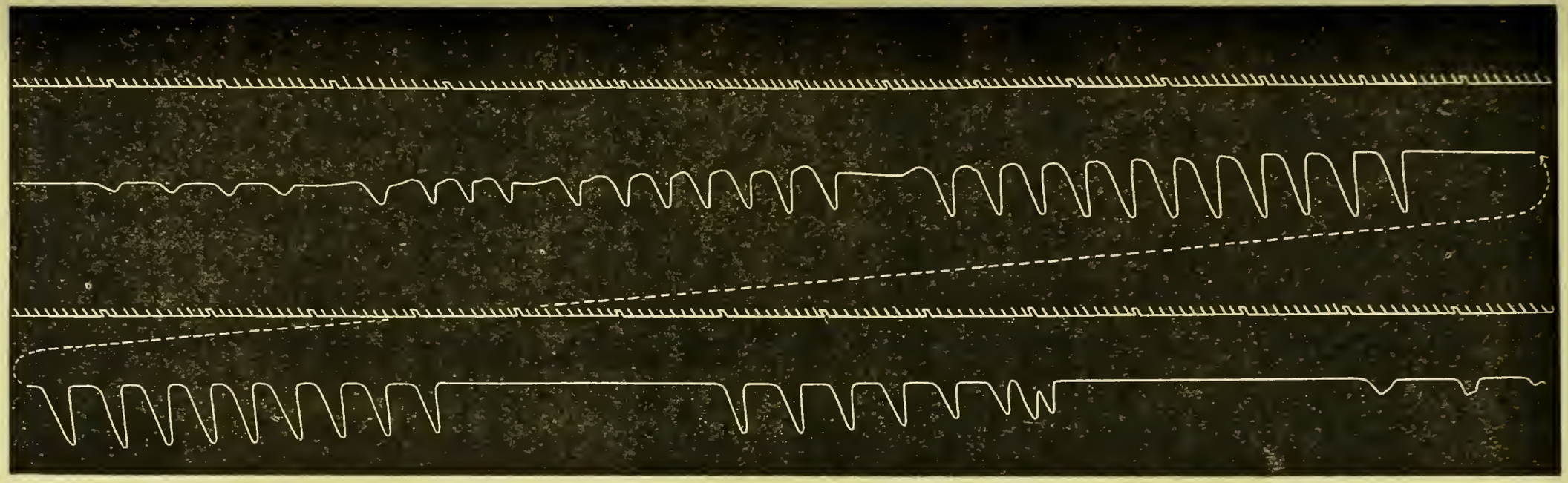
Six minutes later the heart gave this trace :



I then added twenty minims of the iodoform solution, with the following effect :



I then added twenty, fifteen, and twenty minims of the ammonia solution, with the following result :



In this experiment $\frac{1}{5}$ grain of iodoform nearly stopped the heart, and ten minims of a 1 per cent. solution of strong ammonia restored the contractions, so that they became nearly as strong as before the addition of the iodoform. Another $\frac{1}{5}$ grain of iodoform nearly arrested the heart. After twenty minims of the ammonia solution the beats became fairly good again. Another $\frac{1}{5}$ grain of iodoform arrested the ventricle, but a third time its contractions returned on the addition of forty-five minims of ammonia solution, which at last arrested the heart in strong systole, and the trace consequently became arrested above the base line.

In this experiment the same blood was employed throughout, and yet three times iodoform strongly affected the ventricle, and thrice ammonia restored it to good contractions. This experiment surely proves that remedies are mutually antagonistic. This experiment also shows how much more powerfully iodoform acts on the heart than chloroform. One-fifth of a grain of iodoform all but arrested the ventricle, and once did actually arrest it, but half a minim to two minims of chloroform are necessary to arrest the ventricle, and each minim of chloroform weighs about a grain and a half.

THE PRACTITIONER.

JANUARY, 1882.

Original Communications.

CONCERNING THE ACTION OF CHLORIDE OF SODIUM, CHLORIDE OF AMMONIUM, CHLORIDE OF POTASSIUM, BROMIDE OF SODIUM, BROMIDE OF AMMONIUM, BROMIDE OF POTASSIUM ON THE VENTRICLE OF THE FROG'S HEART.

BY SYDNEY RINGER, M.D.

Professor of Medicine at University College, London.

It is generally held that the heart cannot be tetanized, that the application of the ordinary interrupted current gives rise not to a tetanus, but to a rhythmic series of beats.

Ranvier (*Système Musculaire*, 1880, p. 346,) holds that the heart may be tetanized. Says he, the apex of the heart of a frog on the point of dying, if pinched, shows limited and sustained contractions, the analogue of the patches produced by electrical excitation of the stomach or intestine. The point thus pinched becomes pale and depressed below the surface, and this lasts a few minutes, proving that the cardiac muscle can remain permanently contracted, that is, tetanized. Again, he says, if the faradic current is very strong, and the heart sensitive, the heart is thrown into tonic contraction, and this is a tetanus. The same occurs with the apex of the ventricle.

I have often thrown the ventricle into a condition of sustained contraction by applying strong continued faradization to the ventricle in Roy's tonometer, and I find that this condition is more easily induced when the heart is heated to 80° or 90° Fah.

I shall show in this paper that chloride of sodium, and at a certain stage, chloride of ammonium, increase the readiness of the ventricle to become tetanized by faradization. This is not due to weakness caused by the chloride of sodium; for an undrugged heart as it grows weaker is not more easily tetanized.

It is also held that induction shocks sent in at a certain phase of a cardiac cycle, for instance, before the ventricle begins to dilate, are ineffectual; but my experiments show that chloride of sodium so alters the heart, that even before the rise of one contraction is completed a second excitation causes another contraction which rises higher than the first, and that a series of rises, each higher than its predecessor, may be induced by successive induction shocks applied to a ventricle made weak by chloride of sodium.

In the *Journal of Physiology*, Dec. 1881, I have described the effect of hydrate of soda, hydrate of ammonia, and hydrate of potash on the ventricle of the frog's heart. I show that these substances induce a persistent spasm in the ventricle, which, in many cases, remits; and that they weaken the ventricular rhythmic contractions, soda slightly, and by large doses, whilst potash, even in small doses, weakens the ventricle considerably, and soon arrests its beat.

My experiments show also that soda and ammonia increase the irritability of the ventricle, even whilst they weaken it, so that sustained faradization more easily induces a tetanoid state. Potash, on the contrary, lessens the heart's irritability, so that strong and continued faradization leaves the rhythmic contractions either wholly unaffected, or they undergo complete arrest while the faradization is continued.

I now detail certain experiments with salts of soda, ammonia, and potash, to endeavour to ascertain whether the effects of the hydrates is modified, and if so, to what extent, by combination with chlorine and bromine; and further, to ascertain the relative poisonous action of the chlorides and bromides on the heart.

These experiments were made in June with dried bullock's blood dissolved in water, so as to represent normal blood, and to this solution I added saline solution in the proportion of one part of blood to two of saline. Of this mixture I employed

three ounces in each experiment, and added to it from time to time small quantities of a solution of the salt with which I was experimenting.

The tracings run from left to right. The line above the trace indicates the time faradization was continued, and the figure above the line shows the point at which the induction coil stood, in other words, the strength of the electricity.

Chloride of Sodium.

Chloride of sodium affects the heart in most respects like hydrate of soda, but it does not induce any persistent spasm, consequently the trace does not become raised above the base line.

I experimented both with the whole ventricle and with the lower two-thirds of the ventricle, a part free from ganglia. The effect on the part free from ganglia is identical with the effect on the complete ventricle. It is obvious, therefore, that the action of chloride of sodium is exerted through the muscular substance and not through the nervous ganglia.

The effect of common salt is well shown in Trace I., made with the lower two-thirds of the ventricle, and in Traces II. and III. where the whole ventricle was used.

I added a ten per cent. solution to the blood.

Most of the contractions in Trace I. were excited by an induction shock, and these are designated by a star above them. The spontaneous contractions are indication by the letters S P.

Large doses of common salt weaken the ventricular contractions, and as the heart grows weaker the trace rises less and less; but whilst the height of the trace is lessened, its breadth is increased (See Trace I. C and E, Trace II. B, Trace IV. E *c*), the systole though much less complete, is slower in reaching its maximum, and slower in relaxing again. The ventricle as it grows weaker becomes at the same time more easily tetanized by continued faradization. At first, before the heart is weakened, continued faradization produces a normal contraction, and then the heart is held in complete tetanus; thus the rise, like the rise of an ordinary rhythmic contraction, is sudden, and on the discontinuance of faradization the fall is just as sudden. When the heart is considerably weakened, the rise is gradual and wavy, each wave corresponding to a

contraction (See Trace I. B and C; Trace III. A). The effect of succeeding contractions are piled one on the top of the other, and the tetanus trace rises much higher than previous rhythmic traces (See Trace I. B, C, and E; Trace II. B).

Sometimes a similar result is seen in a spontaneous contraction, one contraction beginning before the previous one is finished, and the second contraction rises higher than the first (See Trace I. E *a*). Next I tested the effect of an induction shock, administered just when a contraction had reached its maximum. When the ventricle is weakened by chloride of sodium and does not empty itself, I find that an induction shock applied just when the effect of a previous one is at its height, will excite another contraction, which causes the ventricle to contract further, and a third induction shock produces a still greater contraction, and so on, till at last the ventricle becomes completely closed. We get the effect of one contraction piled on the top of another, and the second contraction begins before its predecessor has begun to relax, nay, even before it has reached its maximum. This effect is well shown in Trace IV. *a a a*. Before the ventricle becomes very weak, two contractions complete the rise; but when the heart grows weaker, six or seven contractions are required to complete the rise.

After comparatively small doses of chloride of sodium the tetanus trace is incomplete, and is slightly undulating at its summit (Trace I. B and C; Trace II. B; Trace III. A; Trace IV. B). Larger doses make the summit of the trace quite straight—like a tetanus trace of a skeletal muscle (Trace I. D, E, and F). Sometimes the commencement of the trace of a contraction is straight, but after a time becomes undulating (Trace II. B).

Part of Trace I. was taken whilst the cylinder revolved quickly. The slight break in the line just before the rise and before the fall, indicates the time when the faradization was poured into the ventricle, and when the faradization was discontinued. The contraction begins almost immediately the electricity is applied, but the contraction does not relax till a quarter, or half a second after the stimulus is discontinued. In Trace III. B, I give the effect of faradization continued for more than nine minutes. This differs from many other traces of prolonged faradization since the tetanus intermitted.

Chloride of Ammonium.

Chloride of ammonium, though more allied in its action to chloride of potassium, is in all essential respects intermediate between chloride of sodium and chloride of potassium.

Chloride of ammonium is a much more powerful paralyser of the ventricle than chloride of sodium, for in four experiments an average dose of twenty-eight minims of a ten per cent. solution stopped the ventricle.

At first the salt affects the trace like caustic soda and caustic ammonia. It greatly prolongs each contraction, and the diastolic dilatation is much lessened, so that the trace rises high above the base line. If the rhythmic contractions are infrequent, there is a rise in the long diastole.

On addition of more of the solution the trace soon changes its character, and the trace of a rhythmic contraction neither rises so high nor continues so long; so that its apex becomes sharp-pointed. The trace rises less and less, and at last the ventricle stops in diastole, and the trace ends close to the base line.

Chloride of ammonium at first increases the effect of continued faradization, so that the trace becomes just like a true tetanus trace, in this respect being like the trace of common salt; but later, when the ventricle begins to grow weaker, even strong continued faradization produces no effect; and later still, like potash and chloride of potassium, it arrests the rhythmic contractions.

Chloride of Potassium.

Chloride of potassium affects the ventricle much like hydrate of potash. It is a powerful paralyser of the ventricle; the height of the trace quickly growing less till the heart ceases in diastole. Shortly before the ventricle becomes quite paralysed, diastolic contractions occur, and thus, unlike soda, potash on combining with chloride does not entirely lose its power to excite continuous spasm in the ventricle.

Like hydrate of potash, the chloride also lessens the readiness of the ventricle to become tetanized on the continued

application of faradization. The effect of both the hydrate and the chloride in this respect is most singular when contrasted with the effect of the soda salts.

Chloride of potassium, like hydrate of potash, affects the ventricle somewhat differently in different experiments. In some the ventricle is made insensible to powerful induction shocks, or the continued application of powerful faradization, the spontaneous contractions continuing the same as before the faradization (Trace V. A and C). On other occasions, and sometimes in the same experiment, faradization arrests the beats, which commence again when the faradization is discontinued (Trace V. B).

Chloride of potassium is more poisonous to the ventricle than chloride of ammonium, and far more than chloride of sodium. Fifteen minims of a ten per cent. solution of chloride of potassium on an average arrest the ventricle, whilst twenty-eight minims of chloride of ammonium solution are required; but 260 minims of chloride of sodium solution did not completely stop the ventricle.

The gradual addition of any of these salts affects the heart much less than when the whole quantity is added at once. A dose which affects the heart but little, if added by degrees, will arrest the heart permanently, or at all events temporarily, if added all at once to the blood.

These experiments show that the effect on the heart depends on the percentage amount of the salt, not on the amount sent to the heart. For instance, after the heart has been arrested, even for ten minutes, the addition of saline solution to the circulating blood will quickly restore good spontaneous contractions, but the heart is receiving the same amount of the salt, but only in a dilute form.

Both chloride of potassium and chloride of ammonium give a slight alkaline reaction, due no doubt to a slight amount of free alkali. It occurred to me that some of the effects of the salt might be due to the minute trace of free alkali. Therefore I made the solution very faintly acid with hydrochloric acid, and on another occasion with acetic acid. However, these acid solutions of chloride of potassium, or of chloride of ammonium act just like the alkaline solutions.

Bromide of Sodium, Ammonium, and Potassium.

These salts affect the ventricle in all respects like the corresponding chlorides; hence it is unnecessary to give tracings of their action.

I find that 300 to 500 minims of a five per cent. solution of bromide of sodium greatly weakens the ventricle.

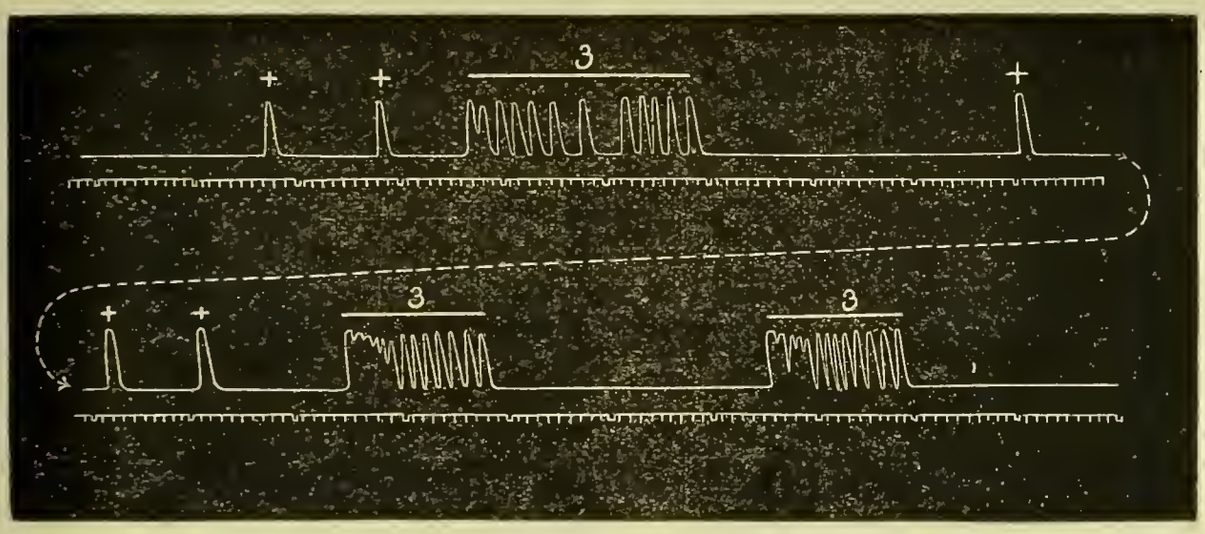
Bromide of ammonium is much more poisonous. In nine experiments the heart was arrested on an average with sixty-six minims of a five per cent. solution.

Bromide of potassium is still more poisonous. In eight experiments I find that the average dose of thirty minims of a five per cent. solution will arrest the heart.

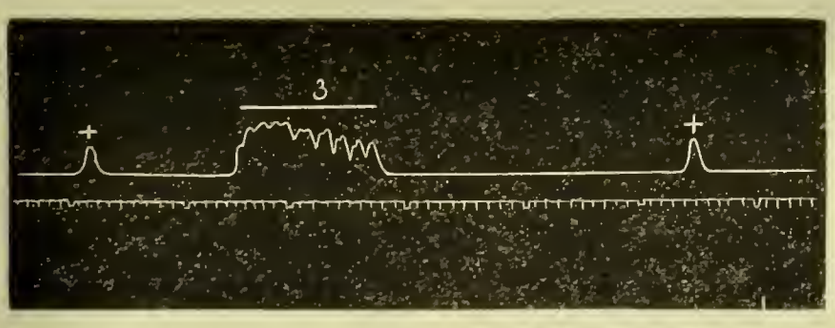
It is obvious, then, that if bromide of sodium is as therapeutically active as bromide of potassium, that bromide of sodium is preferable, from its weaker action on the heart.

EXPLANATION OF TRACES.

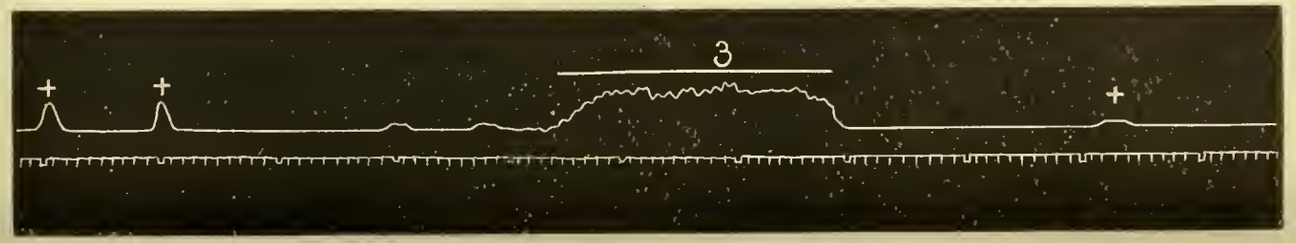
Trace I.—With the Lower Two-thirds of the Ventricle.



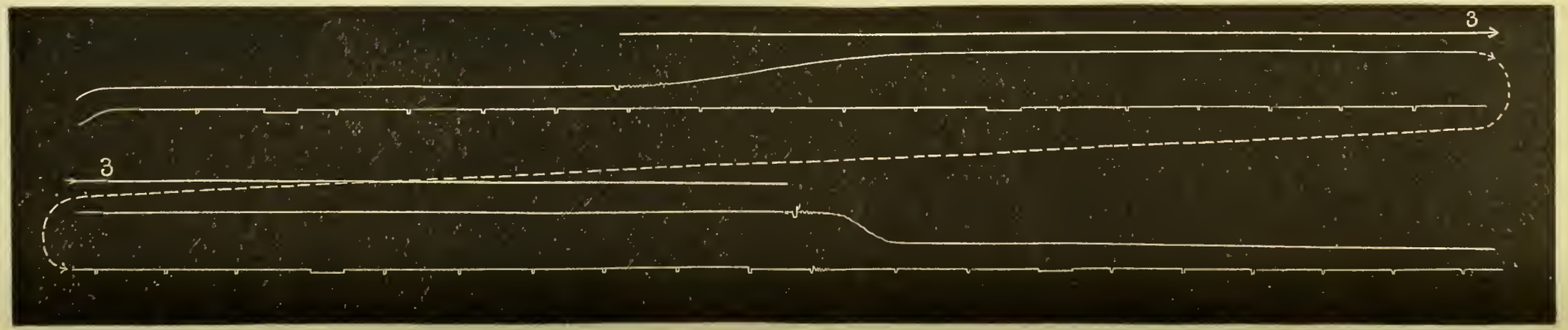
A, before the addition of chloride of sodium to the circulating blood.



B, after 120 minims of a ten per cent. solution.

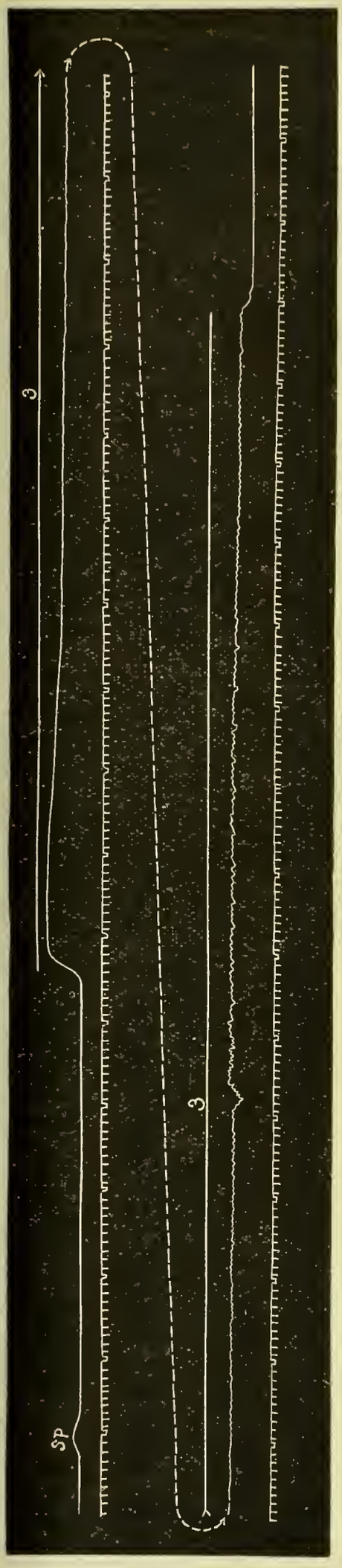


c, after 180 minims of the solution.



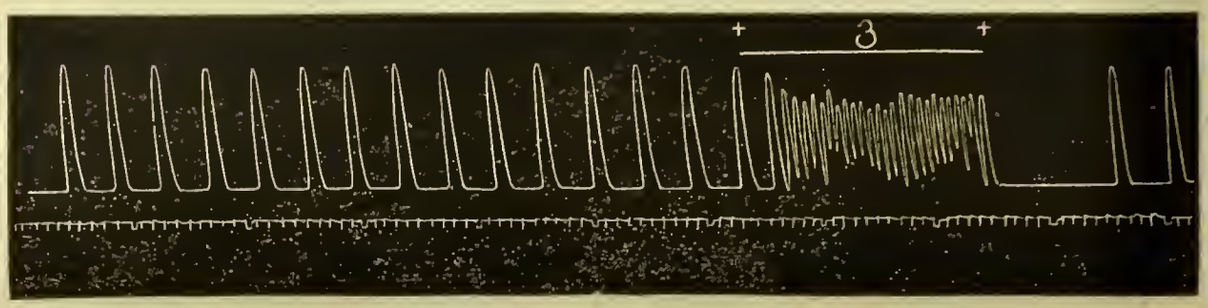
d, trace with the cylinder revolving much quicker. The slight break in the trace shows the time when the faradization was begun, and when it was ended.

E.

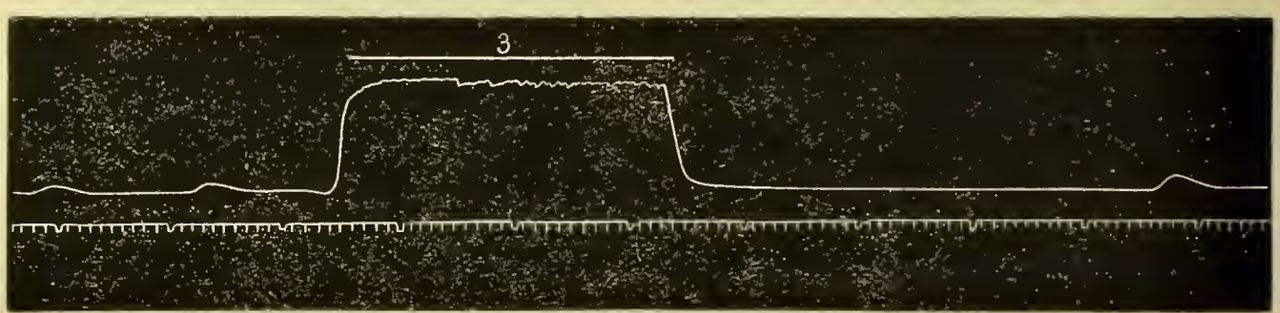


F, after 260 minims of the solution.

TRACE II.—WITH THE COMPLETE VENTRICLE.

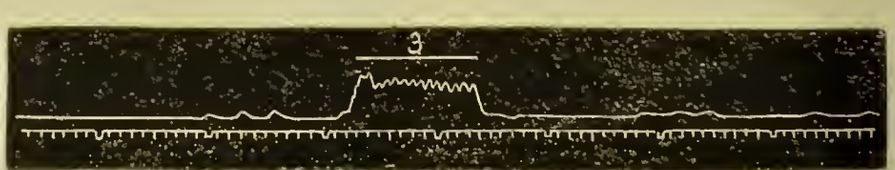


A, before the addition of chloride of sodium to the blood.

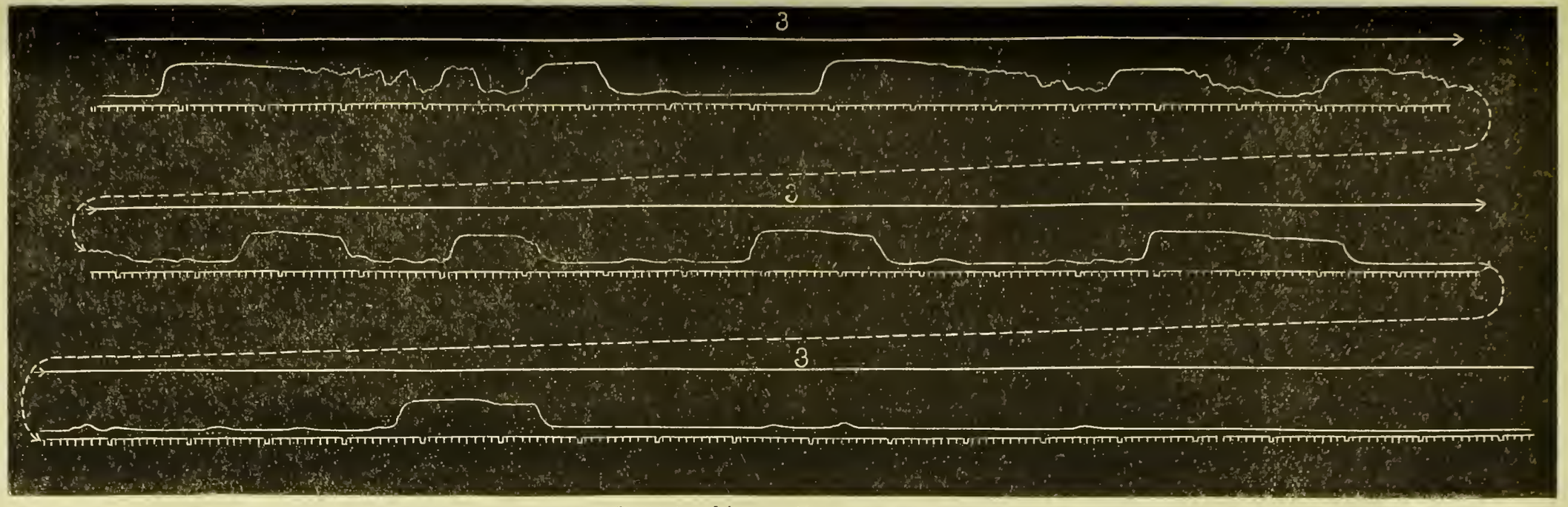


B, after 180 minims of the solution.

TRACE III.—WITH THE COMPLETE VENTRICLE.

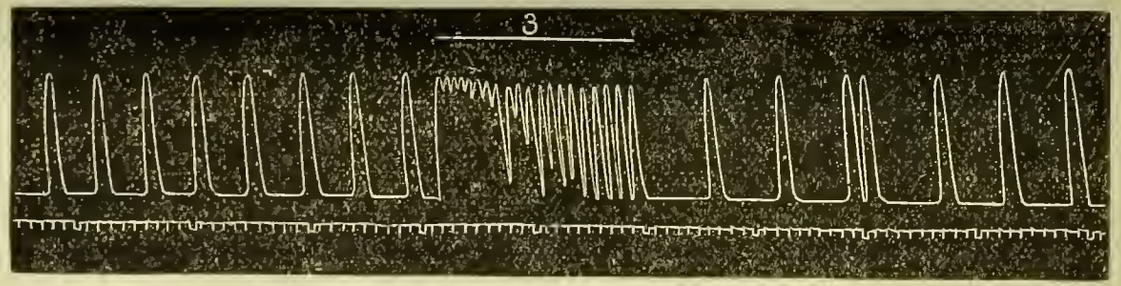


A, after 13 cubic centimetres of the solution of chloride of sodium

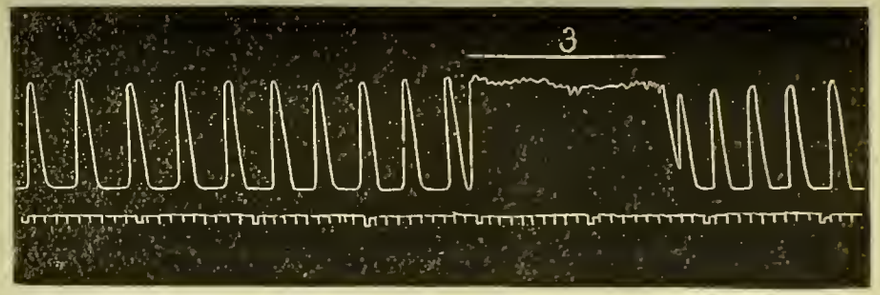


B, after 14 cubic centimetres of solution.

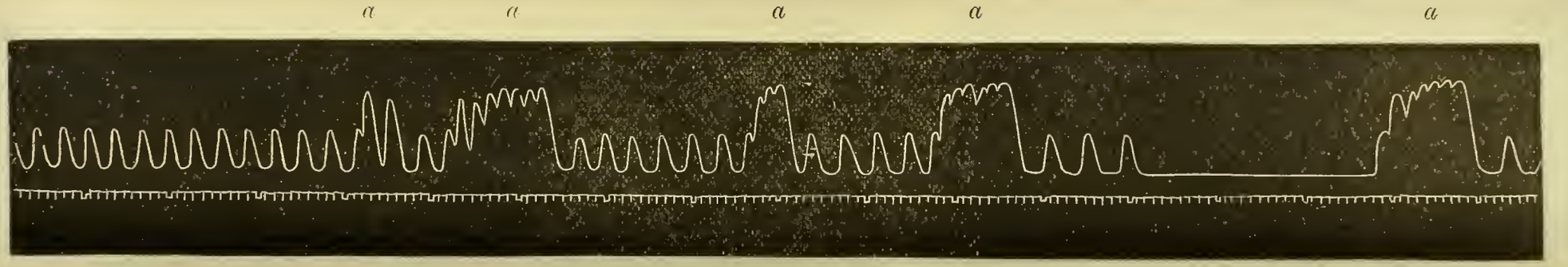
TRACE IV.—THE INDUCTION COIL STOOD THROUGHOUT AT THREE.



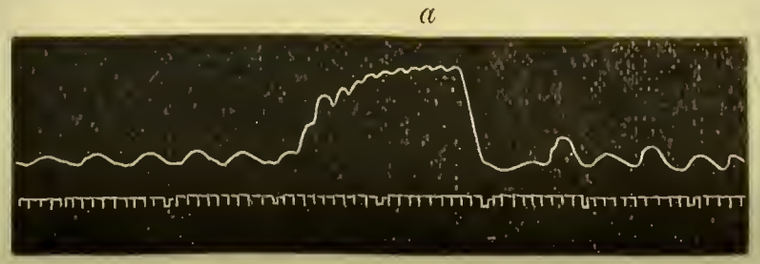
A, before the addition of chloride of sodium.



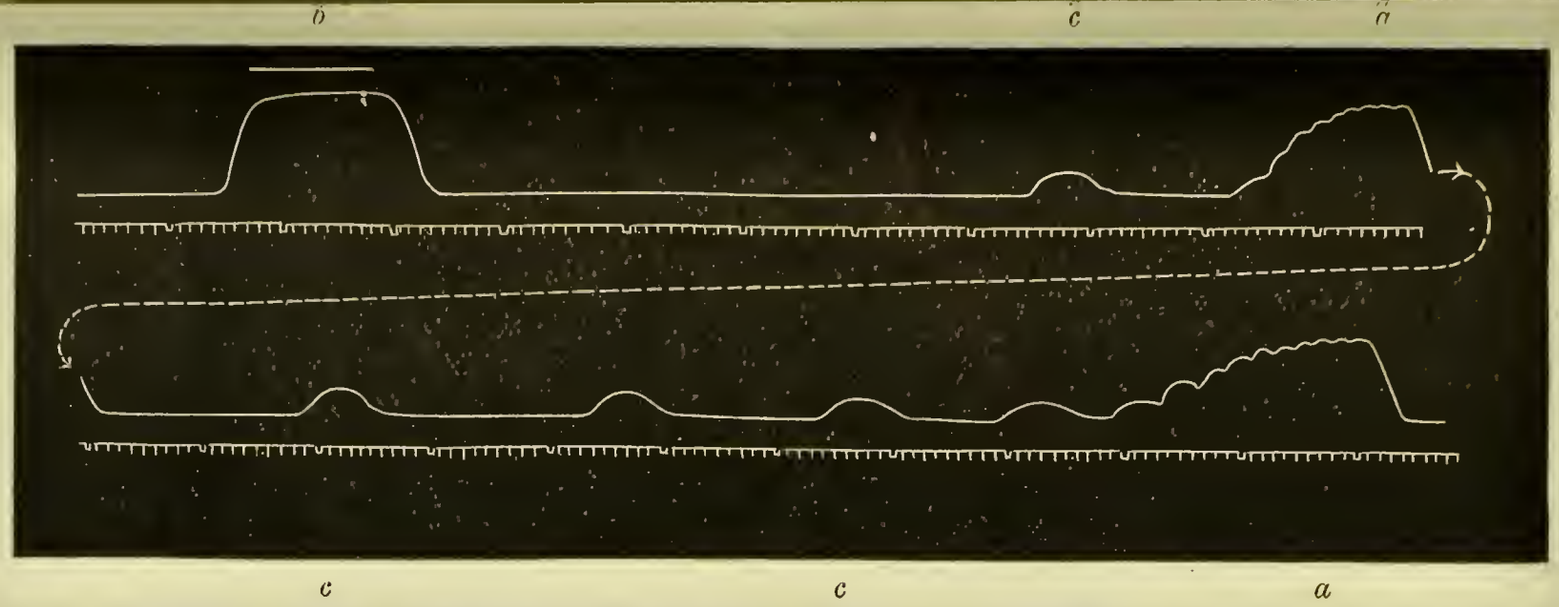
B, after 120 minims of a ten per cent. solution.



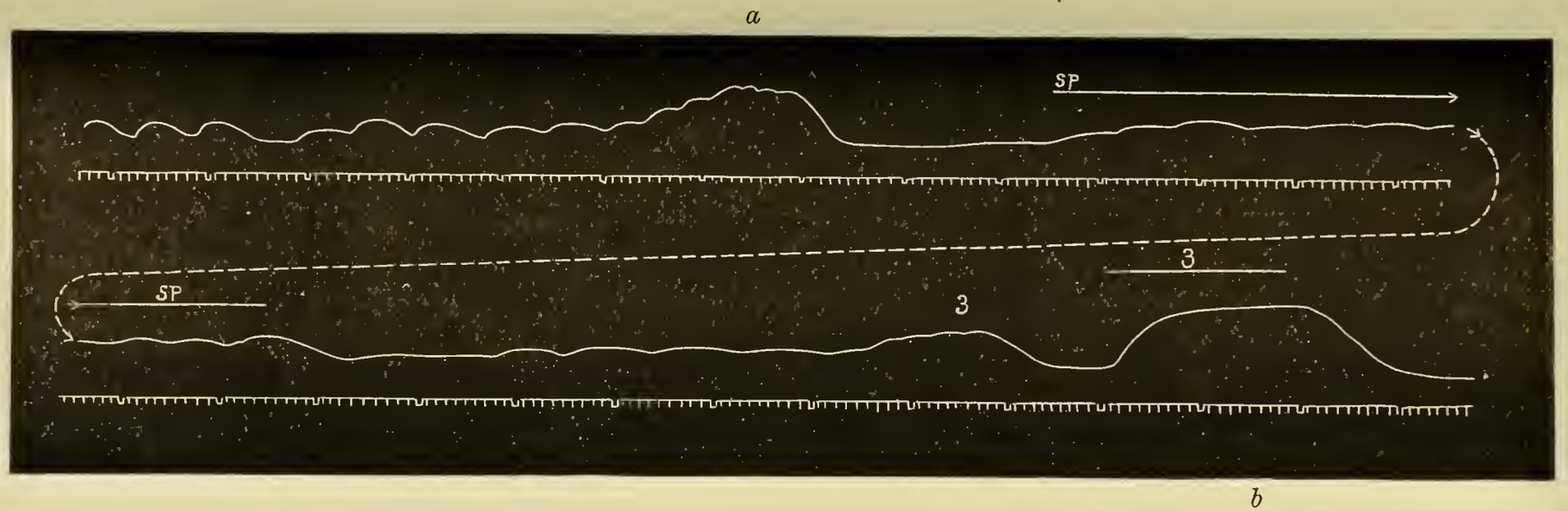
C, in C, D, E, and F, at *a a a*, each undulation in the rise was excited by an induction shock.



D, after 200 minims of the solution.

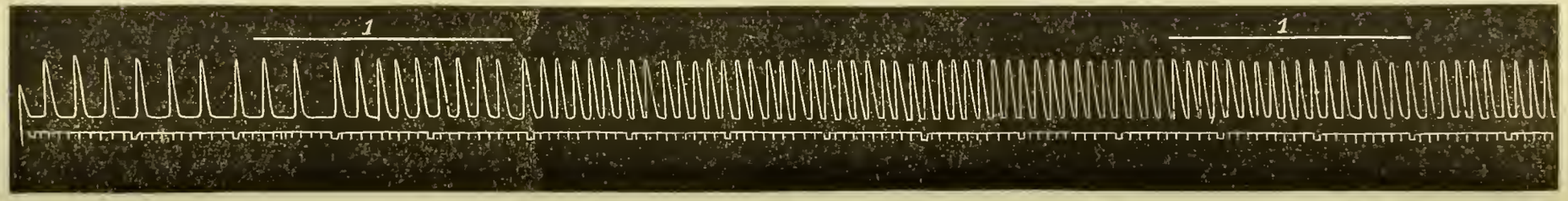


E, after 220 minims of the solution ; *c* are spontaneous contractions.

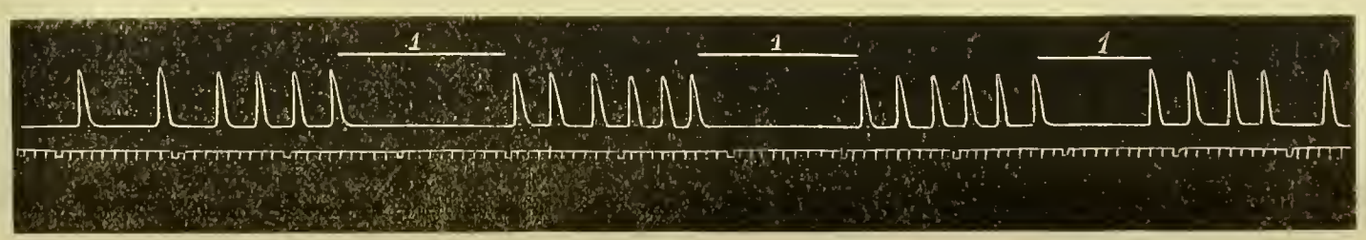


F, in C, D, E, and F, at *a a a*, each undulation in the rise was excited by an induction shock.

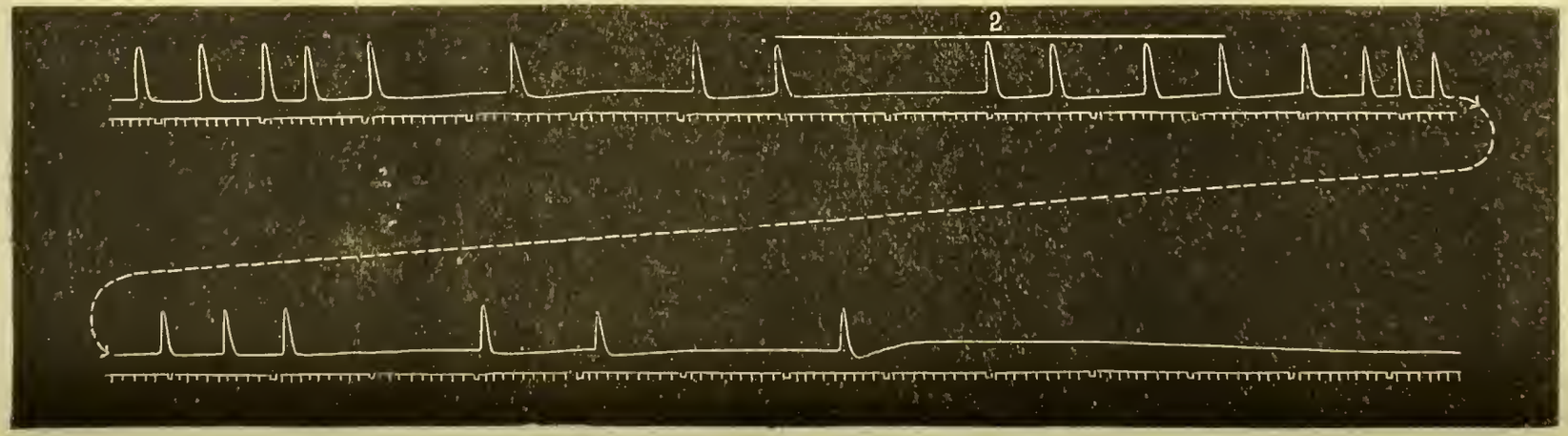
TRACE V.—WITH THE COMPLETE VENTRICLE.



A.



B.



C.

A, B, and C, after the addition of solution of chloride of potassium to the blood.
C, after the addition of 0·9 cc. of ten per cent. solution of chloride of potassium.

THE PRACTITIONER.

AUGUST, 1882.

Original Communications.

ON THE INDIVIDUALITY OF ACTION OF THE COMPONENT PARTS OF A DRUG.

BY SYDNEY RINGER, M.D.,
Professor of Medicine at University College;

AND HARRINGTON SAINSBURY, M.D., M.R.C.P.

THE present paper, though complete in itself, is in some respects a sequel to a paper On the Action of Salts of Potash, Soda and Ammonia, on the Ventricle of the Frog's Heart, read before the Medico-Chirurgical Society, June 13, 1882.

A few words on the subject of the spontaneously beating heart may preface the consideration of the subject proper of this present paper.

A ventricle beating spontaneously may be considered under two aspects. It beats *at a certain rate*, it beats with *a certain force*. The tracing which such a heart gives with the apparatus here employed, and subsequently detailed, shows this *contraction rate* or *rhythm*, and also by means of the height of the trace the *completeness of each individual contraction*, if not the force of each contraction. We have, then, these two elements for consideration, "*contraction rate*," and "*contraction height*."

In the previously mentioned paper it has been shown that that which underlies and is measured by "contraction height" must

be dissociated from that which underlies and is measured by "contraction rate," inasmuch as either may be influenced independently of the other. For the above underlying elements the terms "*contractility*" and "*excitability*" were respectively substituted. The latter term it was found necessary to define, since without such, more was implied than the experiments justified. It has been held and taught that the ventricle of the frog's heart is capable of showing rhythmic contractility apart from any nervous structures—still more recently this view has again been called in question; and whilst the property of responding to stimulation by contraction has been limited to muscular tissue, that of regulating the supply of stimulation has been assigned to nervous tissue. However this may be, the experiments detailed in the previously mentioned paper do demonstrate the presence of TWO underlying elements.

Of these, the one answering to contractility is obviously muscular in nature. The other, answering to excitability, is of more doubtful nature; still, whether generating the stimulus or not, it apparently has to do with the supply of the stimulus, and in this respect is like nervous tissue. For the sake of simplicity, then, the term nervous may be perhaps applied to that element which underlies contraction rate, though it will be clearly understood that the only grounds on which this name is here applied are those of similarity of function.

Since Dr. Gaskell's paper, more care has been taken in the application of the ligature, so as to secure this as nearly as possible in the auriculo-ventricular groove; in many cases no trace of auricle could be seen below the ligature, yet these ventricles have behaved precisely like those others in which more or less of the auricle was below the ligature. The ligature has in all cases been drawn as tightly as the thread would permit, and it is difficult to conceive that the force employed should be unable to destroy any physiological connection between the parts above and those below the ligature.

We now come to the determination of a point incidentally touched upon in the paper already cited, viz., the determination of the "individuality of action of the component parts of a drug."

The question here to be considered is whether one element or

group of elements present in a series of compounds does manifest itself by imparting a uniformity of action to such compounds, or whether each compound acts as a whole, the component elements not being recognizable.

Clinical experience would certainly be to the effect that certain elements and groups of elements do retain their individuality of action to a greater or less degree, but clinical experience is neither simple enough nor definite enough to be able to thus set the question at rest.

The experiments were made with a Roy's tonometer, which, by means of a double cannula, to the end of which the ventricle of the frog's heart is secured, allows of a circulation being maintained through the ventricle by simple syphon action. The heart itself is immersed in an air-tight oil chamber completely filled, a movable bottom, to which a lever is attached, is forced upwards by the atmospheric pressure each time the ventricle contracts and empties itself.

The contractions of the ventricle are recorded by means of the lever on the blackened surface of a revolving cylinder. At regular intervals of time, each quarter revolution of the cylinder, the drug was added to the whole mass of blood. The dose was almost invariably the same for each drug, and indeed for each experiment, and was so calculated from previous experiment as to stop the heart within about an hour. The reason for this limitation of time was the avoidance by it of the element of exhaustion.

The circulating fluid consisted of a solution of 8 grammes of dried bullocks' blood in 200 cubic centimetres of a saline solution; this latter consisted of .5 parts of saline solution, ¾ p.c., and 2 parts of water.

Of this blood mixture 100 cubic centimetres (about 3·5 oz.) were taken for each experiment.

The experiments were performed during the months of February, March, and April, 1882.

The common English frog (*Rana temporaria*) was throughout used.

A heart thus prepared, and the circulation started, soon begins (with very few exceptions) to beat, and as a rule within 10 minutes or so from thus starting it has settled down to a uniform

rhythm. The two elements which we then have to note are the characters of each individual beat, and the rate of succession of the beats.

The term "inhibition" will be constantly used in this paper. It may be defined as either *complete arrest* of the spontaneous beats, or marked slowing of these, whilst during the long intervals separating succeeding beats, or during the interval of complete suppression, the ventricle may be still made to contract by electrical stimulation. Thus it means arrest or marked slowing of the spontaneous beats, whilst the ventricle is still electrically excitable.

When the arrest has been complete, the inhibition has been spoken of as complete.

The term "diastolic contraction" will also be frequently employed. It names a form of contraction of a very slow character, which is frequently observed with certain drugs, *e.g.*, the caustic alkalies amongst others. It is observed during the intervals separating spontaneous beats. This phenomenon has been described in the *Journal of Physiology*, Vol. III., No. 3, in a paper on the Action of the Hydrates of Soda, Ammonia and Potash on the Frog's Heart.

The term "*persistent spasm*" has been used synonymously with diastolic contraction.

Lastly, there remains the term "tetanus" to define. By it is meant fusion, more or less complete, of neighbouring beats. If the ventricle of a frog's heart be subjected to continuous faradization, provided the strength of the current, and the rate of interruption be sufficient, there results more or less fusion of adjoining beats. This fusion has been called "*tetanus*," and when spoken of it has been qualified according as the fusion was complete or incomplete.

Salts of the bases potash, soda and ammonia were examined, viz.—

The citrates of potash.

The sulphates of the three bases.

The carbonates and bicarbonates of potash and soda.

These experiments were performed on precisely the same plan as those already detailed elsewhere with other salts of the same three bases, and hence are strictly comparable with these

latter. The results of both series of experiments will be used here in the consideration of the subject in question.

In the comparison of the action of salts one with another, quality of action comes first, and taking potash salts, the action of the hydrate of potash may be first described. Then the action of the various potassium salts may be compared with this, and the modifying influence, if any, of the acid radical in each case noted.

The actual experiments with hydrate of potassium have been detailed in a previous paper; the effect may be summarized shortly. On rhythm the primary effect was variable, as a rule there occurred increased frequency. The secondary effect was, *in all cases, slowing*, passing into inhibition, complete, or all but complete. A very prominent feature in the potash tracings was the diastolic contraction, in the latter stages during inhibition the whole course of this form of spasm might be observed.

Comparing the action of tripotassic citrate, a distinctly alkaline salt, with the previous, it is seen that the inhibition is less marked. It is distinct it is true, but the height of the trace is reduced to a much smaller quantity before inhibition occurs than was the case with potash.

Of persistent spasm the charts show no trace.

Dipotassic citrate, though an acid salt, may perhaps be admitted for comparison, inasmuch as the quantity added was so small that it could not be distinctly made out by test paper whether the blood mixture had become acid.

The results obtained were similar to those given by the tribasic salt; inhibition did occur, but it was less marked than for potash. Here also there was no trace of persistent spasm.

The citric acid series of potassium salts would appear very suitable for testing the influence of the base, since you here have the base presented in three proportions, whilst the acid element remains a constant. But the strong acid reaction prevents the use of the mono-potassic citrate, the blood mixture becoming distinctly acid with the quantity of salt required to stop the heart.

Sulphate of potash. This salt comes nearer to potash in its effect on inhibition; thus in five out of seven cases inhibition was marked; of the remaining two it was moderate in one,

slight in the other. In three out of the seven cases a slight amount of persistent spasm was observed.

Carbonate of potash, K_2CO_3. This salt is of course strongly alkaline. The tracings obtained closely resemble those of potassium hydrate, marked inhibition being the rule, and persistent spasm coming out strongly.

Bicarbonate of potash, $KHCO_3$. The solution of this salt used was alkaline, though less so than the carbonate. The effect on inhibition was well marked, but rather less so than with the carbonate. Thus, out of six cases, in three inhibition was strongly marked; in one it was moderate, in two slight. Persistent spasm was much less marked, being strongly marked in one case only out of the six, slight in two others; absent in the remaining three.

All the salts above mentioned, including the hydrate, modified in precisely the same manner the effect of the continuous faradic excitation applied to the ventricle. Thus whether one started with a strong or slight tetanus, the drug diminished this tetanus from the first, and in the final stages caused actual suppression of the beats during the time of faradization. The potassium salts described elsewhere, viz., the chloride, bromide, and iodide, inhibited strongly, and modified the effect of continuous faradization as above. They did not cause persistent spasm in the doses used.

The salts of potassium, then, hitherto examined, viz.,

The hydrate,
The chloride, bromide, iodide,
The citrates (tripotassic and dipotassic),
The carbonates (the di-and mono-basic),
The sulphate,

Agree qualitatively on the following points:—

They arrest the heart in diastole,

They show a strong tendency to arrest suddenly the rhythmic action of the heart, *i.e.*, to inhibit.

They render the heart less and less susceptible to the effect of continuous faradization.

On the point of the production of persistent spasm they do not agree; it is, however, to be noted here, that it is the least saturated of the salts of potash which exhibit this spasm in the

highest degree, viz., the carbonates, and that of the two carbonates, the one containing excess of the acid radical, viz., the bicarbonate, shows the least degree of spasm.

The production of spasm is to some extent a question of dose, and thus a quantity of a salt, *e.g.* chloride of potassium, which, added gradually, may cause no persistent spasm, may, if added suddenly, cause more or less spasm. This, however, does not affect the question here considered, for the experiments are comparative, and the readiness with which spasm is excited is certainly modified by the acid radical.

In the case of the chloride, bromide, and iodide group, the salts of sodium, ammonium, and potassium have been compared one with the other, and with regard to quality of action it has been shown that the ammonium salts contrast strongly with potassium salts, in that *they do not tend to inhibit*, and further in that their action in lessening the effect of continuous faradization is *less marked.*

The sodium salts of the same group have been shown to stand between potassium and ammonium salts in respect of inhibition, though much nearer to ammonium salts, for their tendency to inhibit is but slight.

With regard to the citrates, similar results were obtained; thus citrate of ammonia was shown *not* to inhibit and *not* to lessen the effect of the continuous faradization applied to the ventricle. Citrate of soda inhibited but very slightly if at all, and did not diminish the effect of continuous faradization.

In the present series, one ammonium salt only, the sulphate [$(NH4)_2S0_4$]) was examined. This salt was very carefully examined and found to be, if anything, slightly acid, therefore any effects could not result from the presence of free ammonia.

Of six experiments, in *no case was there inhibition.* In two cases there occurred well-marked spasm as a primary effect; and in five out of the six cases the beats increased in strength, as a primary effect, the tracing showing increased height, and, as a rule, also increased breadth.

As to continuous faradization, there was no diminution of effect; indeed there appeared to be slightly increased excitability as an early effect of the drug.

The carbonates of ammonium were not taken, on account of their instability and not very definite composition.

Of sodium salts, sodium sulphate did not inhibit, the rhythm remaining so long as the beats were visible.

No persistent spasm appeared.

In the final stage continuous faradization caused the mounting up of the trace already described as occurring with the sodium salts of the chloride group. With sodium sulphate the effect was comparatively slight, but it was distinct.

The effect of continuous faradization was certainly not diminished; if anything, it appeared increased.

Bicarbonate of soda. No inhibition; at any rate in the final stage. The rhythm, in fact, in this final stage being much more frequent than at the start. In four out of the six—preceding this final stage was a stage during which the heart beat in phases.

No persistent spasm appeared.

In the final stage slight mounting-up occurred on continuous faradization. In one case it was very well marked.

Carbonate of soda. No inhibition. Frequency of rhythm, in fact, increased in the end stage.

Persistent spasm very strongly marked.

Slight mounting-up occurred in the end stage on continuous faradization.

With the bicarbonate of soda the effect of continuous faradization became distinctly increased.

With the carbonate this effect was still more marked.

The solution of bicarbonate of soda used was very distinctly alkaline to test-paper, and both this salt and the carbonate in the quantities used appeared in the latter part of each experiment to be dissolving the heart to some extent, there being very considerable oozing from the heart; and when removed at the end of the experiment, the heart feeling distinctly soapy.

This is mentioned here because, in spite of very evident changes affecting the substance of the heart, whether of the nature of solution or not, the rhythm still persisted.

Ammonium salts, then, so far as they have been examined, agree in that they do not inhibit; further, they agree in their primary effect, viz., increase of the force of the ventricular

contractions, together with, as a rule, more or less persistent spasm.

Sodium salts agree in their slight action on rhythm, and also in that with all the salts named; with the exception of the citrate of soda, mounting up occurred in the final stage.

Having compared these salts qualitatively, it remains to put together the quantities used, and see if these make clear the dependence on the base as the essential factor in the action of the drug. If this be so, and the acid radical do but slightly and unappreciably modify the influence of the base, then, confining one's attention to salts of one base, the quantities required of such to arrest the heart will contain equal weights of the basic element, *i.e.* the quantities will stand to one another in the proportion of the molecular weights.

In the following table of quantities, in the column headed "weights containing equal quantities of basic element," the numbers given represent either the molecular weight or the molecular weight divided by the number of atoms of base present. This is of course necessary, for weights of say tripotassic citrate and of iodide of potassium, in the proportion of their molecular weights, would contain three atoms of potassium in the former to one in the latter. The salts examined either did not contain any water of crystallization, or this was carefully removed, so that the solution percentage was calculated for the anhydrous salt.

It was attempted to make the sodium series more complete by including the hydrate, but though the rate of dosage was made very small, so as to extend the experiment over a much longer period than in the case of the others, it was found that the heart still became firmly contracted in systole. At the same time the heart oozed very considerably, causing the pen to fall, and giving to the tracing the appearance as though the heart really had gradually dilated. From the tracing, in fact, one would have concluded that the heart did finally pass into a state of diastole.

QUANTITY TABLE.

Name of salt.	Weights containing equal quantities of basic element.	Actual quantities found, in grains.
Potassium Hydrate	56	1·35
,, Iodide	166	3·16
,, Bromide	119	3·28
,, Chloride	74·5	2 46
,, Sulphate	$87=(\frac{174}{2})$	3·85
Tripotassium Citrate	$102=(\frac{306}{3})$	2·31
Dipotassium Citrate	$134=(\frac{268}{2})$	3·39
Potassium Carbonate	$69=(\frac{138}{2})$	2·0
,, Bicarbonate	100	3·25
Ammonium Iodide	145	6·3
,, Bromide	94	3·7
,, Chloride	49·5	2·93
,, Citrate		
,, Sulphate	$62=(\frac{124}{2})$	2·93
Sodium Iodide	150	84·24
,, Bromide	103	51·7
,, Chloride	58·5	29·77
,, Citrate		
,, Sulphate	$71=(\frac{142}{2})$	55·7
,, Carbonate	$53=(\frac{106}{2})$	22·2
,, [1] Bi-carbonate	84	44 74

In the foregoing table the potassium series, as the most complete, may be best considered. If the numbers experimentally found be compared with those in the molecular weight column, it will be seen that the correspondence is not such as to justify the statement that the potassium element alone rules the effect. With certain of the salts it will be seen that the numbers representing them in either column do stand to one another in somewhere about the same proportion; in other instances the correspondence fails. But just as the correspondence is not sufficient to justify, so the failure of correspondence is not

[1] The number obtained here was in four of the experiments with a five per cent. solution, which was substituted for the ten per cent. solution, as all the salt did not go into solution at this concentration. With the five per cent. solution 50 c.c. only of blood were used.

sufficient to negative the above statement. To set this question at rest a more numerous set of experiments will be needed.

However this may be, one must draw attention to the closeness with which the numbers come out, for this constitutes one of the chief features of resemblance between the potassium salts. Very small quantities are here dealt with, and of course very small errors cause in such cases wide divergence; yet, omitting the hydrate of potassium, which is not ordinarily included amongst the salts of potassium, and which, on account of its extreme alkalinity, does not well compare with neutral salts, it will be seen that 2-4 (3·85) grains will include the extremes of variation. Even these limits include strongly alkaline salts, *e.g.*, the carbonate of potassium and the tripotassium citrate; excluding these, the range of variation is within narrower limits. This qualitative resemblance is the more remarkable when one compares the acid radicals one with the other; thus, between the acid radical of the sulphate and the acid radical in the bicarbonate the difference in quality could hardly be greater. This is perhaps still better seen by comparing the hydrogen salts, viz. sulphuric acid and carbonic acid (H_2SO_4 with H_2CO_3). The difference in properties is extreme; yet neutralize potash with these two acids and the resulting salts, the sulphate and bicarbonate, differ so little in their action that, as tested by the ventricle of the frog's heart, the numbers 3·85 and 3·25 represent their activities respectively.

It must be remembered, as has been elsewhere stated, that the proposition is not that one element or group of elements in a drug alone should act, but that such element or group should be capable of more or less individual action, hence that some degree of uniformity of action should be traceable through a series of salts containing the particular element or group of elements. The salts of potassium, as here tested, certainly seem to bear out this proposition, and side by side with the fact of their resemblance to one another in containing the same element—potassium—must be placed their similarity of action, qualitative and quantitative, whether the conclusion be drawn that such connection is of cause and effect or not.

So far as examined the salts of ammonium and of sodium show a similar resemblance in their action.

The question is one of great importance, and very practical in its outcome, for if such one-sided action do hold, then it is clear that, given the element or elements we wish to use for their special effect, we shall choose for the other side of the drug the least active elements we can find; thus, supposing that on certain tissues the iodine be the active agent we desire, and we have the choice of combining this with sodium, ammonium, or potassium, we shall choose the first. We thus shall have some rule to guide us in the choice of drugs, till actual experiment in each case determine whether the action of one side is all we require, or whether in the particular case in question we need the action of both sides.

It may be mentioned that the metals of the alkalies, sodium, potassium, ammonium, have special importance in that their salts as a rule are soluble, and hence suitable for internal administration.

It is necessary, in order that misunderstanding may not occur, to lay stress on the statement already made, that individuality of action of the component parts of the drug is the sole contention. It is true that the experiments here which give for potassium bromide and potassium bicarbonate almost identical figures, would seem to indicate that one side of the drug alone was active, that the bromine and the carbonic acid formed no part of the characteristics of the drug named. Clinical evidence negatives such a conclusion very decidedly. Thus the bromides of the three bases, sodium, ammonium, potassium, show a similarity of action which can scarcely be explained, excepting on the ground of their containing in common the element bromine. The same may be stated for the iodides, whilst for the element chlorine, clinical evidence would seem to point to its activity in the compounds of the marsh gas series, to which chloroform and bichloride of methylene belong.

Clinical evidence, then, to go no further, would point to a chlorine, bromine, and iodine action, and indeed without such evidence the proposition is an inconceivable one, that elements of known activity should, on entering into combination with other elements, exert no influence whatever in modifying the activity of these other elements, and yet retain no individual action of their own—in fact, should simply disappear.

The fact that the heart's action, as here tested, is not capable of demonstrating this other side of the drug action remains. No explanation will be here attempted, though it is clear that a scheme such as the present will obviously fail in demonstrating changes which naturally spread over considerable intervals of time, *e.g.* those of growth and decay, which changes certain drugs affect very markedly. As it fails in this respect it may fail in many other directions, and the recognition of but one side of a drug must be set down to imperfection of the *schema*.

In the consideration of this one-sided action of drugs, the actual results obtained, apart from any theory, must not be lost sight of.

In addition to the salts of the three bases, potassium, sodium, ammonium, already examined, others have been added to the series, and these have yielded results in conformity with those already obtained.

For the actual numbers reference must be made to the quantity table. It will there be seen that the ammonium salts come very close to the potassium salts, whilst the gap separating the sodium salts from these two is a very wide one, the latter salts being 10-20 times less poisonous than the ammonium or potassium salts.

Further, as to inhibition, the results here are similar to those already obtained. Potassium inhibits strongly. Ammonium, if anything, appears to act the other way, the contractions growing less and less in value, whilst the rate of contraction is accelerated.

Sodium is near to ammonium; it has, at any rate in the final stages, very little effect on rhythm.

Potassium therefore stands first—as most poisonous; ammonium next; then, with a wide gap between, sodium.

ON THE ANTAGONISM BETWEEN VERATRIA AND POTASSIUM SALTS.

BY SYDNEY RINGER, M.D.,

Professor of Medicine at University College, London.

In some previous experiments published in the *Journal of Physiology*, Vol. III., No. 5, I found that circulating simple saline solution through the ventricle causes it after each contraction to dilate very slowly; in fact the trace is just like the trace of a ventricle poisoned by veratria. I showed also that a small dose of any potassium salt, 1 in 10,000 to 1 in 15,000 parts, will obviate this prolonged dilatation, making the ventricular dilatation normal.

I subsequently learnt that the saline solution supplied to me was made with pipe water instead of distilled water, and on testing the action of saline solution made with distilled water I did not obtain this dilatation. The prolongation of dilatation of the ventricle is therefore due to some of the constituents in the pipe water. The water used in making my saline solution was supplied by the New River Water Company, and contains the following inorganic constituents in a million parts: calcium, 38; magnesium, 4·5; sodium, 23·3; potassium, 7·1; combined carbonic acid, 78·2; sulphuric acid, 55·8; chlorine, 15; silicates, 7·1; free carbonic acid, 54·2.

I have made numerous experiments which clearly show that the minute trace of lime in this water is the cause of the prolonged ventricular dilatation.

The effect of a minute quantity of a potassium salt in removing or preventing lime salts prolonging the diastolic dilatation of the ventricle, naturally led to experiments to test whether

potash salts can prevent veratria prolonging the ventricular dilatation.

These experiments were made with a Roy's tonomer.

In each experiment I used 100 cc. of blood mixture, made by dissolving dried bullock's blood, so as to represent normal blood, diluted with four parts of saline made with New River water.

The potassium chloride solution contained 1 per cent. of the salt.

I find that a small dose of potassium chloride will completely obviate the effect of veratria and restore normal contractions.

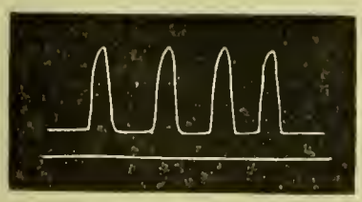
On June 12, after taking a normal trace, I added to the 100 cc. of circulating blood mixture 1 cc. of 0·2 per cent. solution of veratria, which produced well-marked veratria effects. About twenty minutes after the dose of veratria I added 2 cc. of potassium chloride solution, and in about half a minute this greatly lessened the veratria effects. Then from time to time I added more of the potassium chloride solution, and after the addition of 5 cc. the contractions became normal and only a little weaker than the contractions previous to the addition of veratria. On June 13 I neutralised the effect of 5 cc. of 0·2 per cent. veratria solution by adding to the veratrised circulating blood mixture 3 cc. of 1 per cent. solution of potassium chloride.

On the same day, after taking a normal trace, I added to the circulating blood mixture 2 cc. of 0·2 per cent. solution of veratria and produced a well-marked veratria effect. Five cubic centimetres of potassium chloride solution completely counteracted the veratria, and restored good normal contractions. About forty minutes later I added a second dose of 3 cc. of veratria solution and a second time produced marked veratria effects. I then added a second dose of 3·5 cc. of potassium chloride solution, and a second time counteracted the veratria and restored normal contractions equal to the contractions at the beginning of the experiment when the unpoisoned blood mixture passed through the ventricle.

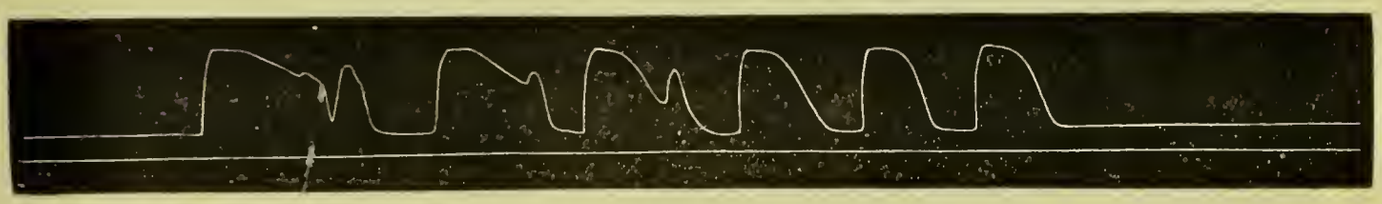
On another occasion, after taking a normal trace, I added to the circulating blood 1 cc. of 0·2 per cent. veratria solution, with 3 cc. of solution of potassium chloride, and the contractions

continued unaltered. Then I added three successive doses of 1 cc. veratria (0·2 per cent.) solution, making 4 cc. in all. This produced a moderate veratria effect. Then I added 1 cc. of potassium chloride solution, and counteracted the veratria, but the contraction became weaker.

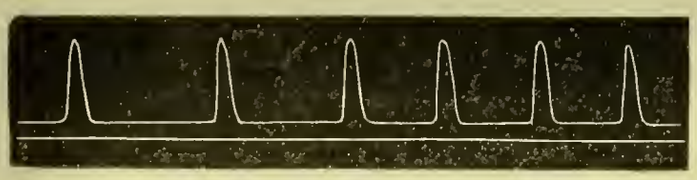
On June 14, after taking a normal trace, I added to the circulating blood mixture 3·2 cc. of 0·2 per cent. solution of veratria. This large dose of course produced well-marked veratria effects, which were entirely removed by 5 cc. of the potassium chloride solution.



A



B



C

DESCRIPTION OF TRACINGS.—A, trace with blood mixture ; B, trace after the addition of 3·2 cc. of 0·2 per cent. solution of veratria ; C, trace after the addition of successive doses of 1 per cent. potassium chloride solution, 5 cc. in all.

Observations on the Relative Effects of Certain Members of the Ethylic Alcohol Series on the Ventricle of the Frog's Heart.

By SIDNEY RINGER, M.D.

AND

HARRINGTON SAINSBURY, M.D., M.R.C.P.

[From the *Practitioner*. Vol. xxx., page 339.]

The object in view in the following experiments was to determine the relative physiological activity of certain members of the above series. The ventricle of the frog's heart was chosen as the test tissue. The dose of any particular alcohol requisite to abolish the functions of this tissue gave the measure of the activity of this alcohol. The following alcohols were taken : methylic, ethylic, propylic, butylic, amylic—the normal alcohols of the first three were selected ; of the last two the isomerics were taken, viz., iso- and pseudo-butyl alcohol and iso-amyl alcohol. In addition to these, iso-propylic alcohol was experimented with.[1] The first three members alone of the series are consequently more strictly comparable if the object in view be the relation between molecular constitution and physiological activity. But from a practical point of view the whole series must be brought in, for, of the above, propylic, butylic, and amylic alcohols constitute for the most part

[1] The alcohols, with the exception of the methylic and ethylic, were obtained from C. A. F. Kahlbaum of Berlin. Normal butyl alcohol, being obtainable with some difficulty, was not taken ; the iso-amyl alcohol examined was the amylic alcohol of fermentation, and commonly goes under the name of amylic alcohol ; it is, however, one of the iso-primary alcohols, or a mixture of two such.

the fusel oil which contaminates beer, wine, and spirits. Fusel oil is a by-product of fermentation, and, owing to the higher boiling-points of its constituents, alcohols, it contaminates principally the last products of distillation; amylic alcohol is its chief constituent. Rapid fermentation at comparatively high temperatures favours the production of fusel oil.

It is on the grounds of the presence of these higher alcohols, as impurities of ordinary alcholic drinks, and of the widespead use of the latter, both as articles of diet and as medicine, that the determination of the relative physiological activity of these impurities has a distinctly practical bearing.

The literature on the subject of the influence of alcohol (ethyl-alcohol) on the circulation is, from a physiological point of view, very incomplete. The position alcohol occupies is that of a narcotic, and it is probable that its action is very similar to that of ether. The effects of moderate doses in augmenting the force of the heart's contractions and increasing the pulse frequency are well established. The sphygmographic experiments of Parkes and Wollowicz on man showed clearly the accelerating effect, but they gave no distinct indication of increased arterial pressure.[1] Nothnagel and Rossbach[2] state that after toxic doses of alcohol there may be a fall in the pulse-rate of one twentieth and in the blood pressure of one-sixth. They state that this is probably in part a reflex effect, in part a direct effect on the cardiac apparatus and vagus centre. Section of the vagi during such, according to the same authors, causes a rise in the blood-pressure and pulse-rate; when the heart action is reduced to the minimum all the peripheral vessels are found widely dilated. The above are probably the results of Dr. Zimmerberg's experiments which we find quoted in Wood (*op. cit.*). These experiments of Zimmerberg were with very large

---

[1] Wood's *Therapeutics*, 1881, art. "Cardiac Stimulants," p. 119.

[2] *Handbuch der Arzneimittellehre*, 1880.

doses. According to Dogiel[1] arterial pressure is at first increased, then lowered, whilst the pulse rate shows three stages: first of increase, then of slowing, and finally again of increase.

We may take it, then, that experimental evidence is in accord with clinical experience and indicates a primary stage of stimulation which gives way to one of paralysis as the dose increases.

With respect to the other members of the alcohol series, Nothnagel and Rossbach (*op. cit.* p. 340) state that the first five members, viz., from the methylic to the amylic inclusive, have been examined, and that their action is the same in quality as that of ethylic alcohol, but that in degree they are poisonous in ascending order, methylic being the least poisonous, amylic the most poisonous. They further give a definite numerical ratio, and state amylic alcohol to be thirty times as strong as the methylic, fifteen times as strong as the ethylic.[2] But beyond this rather bare statement there is nothing, and, in the absence of the original paper, the statement in itself is both wide and vague. There are in all four butylic alcohols, each having the empirical formula $C_4A_{10}O$; of these, two are primary alcohols, one is secondary, and one is tertiary. Similarly, the empirical formula, $C_5H_{12}O$, of the amylic alcohol is capable of eight possible arrangements; of these, six are actually known, viz., two primary alcohols, three secondary, and one tertiary.[3] The indefiniteness of the term amyl or butyl alcohol is thus apparent. In the absence of positive statement, however, it is more than probable that the amylic alcohol employed by Gros was the ordinary amylic alcohol of fermentation, which Pasteur has shown to be a mixture of two isomeric alcohols,[4] both of which are

---

[1] Wood, *loc. cit.*

[2] This is given on the authority of "Gros" without any further reference. In the Index Catalogue a thesis by A. F. A. Gros, "*L'action de l'Alcool amylique sur l'Organisme*," Strassbourg, 1863, is recorded. The paper itself we have not been able to get at.

[3] See Fowne's *Chemistry*, ed. by Watts, 12th ed. 1877.

[4] *Op. cit.* p. 149.

primary alcohols. Similarly, the butylic alcohol, if not the normal, would almost certainly be the fermentation alcohol, viz., isobutyl alcohol, and the consideration would again be restricted to a primary alcohol. But the differences chemically between two primary representatives of a particular alcohol, *e.g.*, amylic, are much less than between a primary and a secondary, or between a primary and a tertiary, or between a secondary and a tertiary; and so in the absence of the normal alcohol this latter is most nearly represented chemically by its primary isomeric. Hence, we may take it that Gros's statement refers to the normal methylic, ethylic, propylic alcohols, and to the primary butylic and amylic alcohols if indeed it does not refer to the normal alcohols of these latter two; this, however, is unlikely. We may state, with reference to the present series of experiments, that they were completed before we had come across the statement of Gros, hence there was no preconceived notion as to a particular physiological relation.

The narcotic effects of the higher alcohols are stated to last much longer than those of the lower,[1] and it is also stated that the effects of alcoholic drinks with much fusel oil are characterised by their much stronger action in degree, not by a difference in kind. Results very different to these were obtained by T. Schlossberger[2] from experiments on cats, dogs, and rabbits; these were in part undertaken with Professor Griesinger. In the original paper it is stated that chemically-pure methyl and amyl alcohols were employed, but no further details on this point. The action of both is stated as quite similar to that of ethyl alcohol, but that with regard to energy absolute ethyl and methyl alcohols are scarcely surpassed by amyl alcohol. The evidence is, however, very incomplete and by no means convincing.

The present experiments were made with Roy's tonometer; the circulating fluid consisted of a solution of desiccated bullock's blood in water of about the concentration of normal blood; this was further diluted with two

[1] Richardson, quoted by Nothnagel and Rossbach, *op. cit.*

[2] *Annalen d. Chemie u. Pharmacie*, lxxiii. p. 213, 1850; also *Journal of Chem. Soc.* vol. iii., p. 180.

and a-half times its volume of saline, 0·6 per cent. The ligature was applied as nearly as possible in the auriculo-ventricular groove. The heart thus fed with the blood mixture as a rule began soon to beat spontaneously. At definite intervals of time the drug was now added to the whole mass of the circulating fluid. The dosage was maintained uniform, and was such as previous experiment had shown to be sufficient to arrest the heart within an hour approximately. The restriction of the time was for the purpose of eliminating the error due to the natural process of dying.

The functions of the ventricle were in each case completely abolished by the end of the experiment, so that the ventricle neither beat spontaneously nor responded to electric excitation. Break shocks were alone made use of for excitation.

On the subject of these alcohols two sets of experiments were undertaken. The first series were made in the summer and autumn months of 1881 ; the second series in November and December, 1882, and February, 1883. The first series comprised the whole range of alcohols, viz., methylic to amylic inclusive ; the second included only the first three—methylic, ethylic, propylic ; the experiments with these three were repeated because, in the first series, these alcohols had not been pushed to complete abolition of the ventricular functions.

The latter series will be given first, and the list completed from the first series, the last two members of which were pushed as in the second series to complete abolition of the cardiac functions.

Methylic alcohol, CH_4O. The pure, absolute alcohol, as with each member of the series, was used. The following quantities were required :—

	° of Room.	Quantity.
Nov. 25	17° C.	11·4 cc
,,	11° C.	12·6 cc.
Nov. 27	15° C.	12 cc.
,,	16° C.	11·4 cc.
Nov. 29	15° C.	12 cc.
,,	15° C.	13·2 cc.
		72·6 cc. ∴ Av. = 12·1 cc. = 205·5 minims.

The heart was arrested in diastole.

As to the effect on frequency of contraction nothing special was to be noted, except towards the end stages, when, in every case, spontaneous action ceased completely, whilst the heart could still be made to contract on stimulation.

The breadth of the trace, *i.e.*, the duration of the beat, became immensely broadened out in the end stages.

The effect on the latent period of the beat was doubtful. The "period of diminished excitability," or "refractory period" of Marey, was apparently slightly shortened—certainly it was not increased.

The effect of continued faradization applied to the ventricle diminished under the influence of the drug, *i.e.*, the ventricle became less excitable for this mode of stimulation.

The effect of diluting the poisoned circulation with its own bulk (100 cc.) of fresh saline, 0·6 per cent. was, in one case to cause quick recovery, but the restored beats retained their greatly-prolonged character. In a second case slight recovery appeared at the end of half revolution, some four minutes, the restored beats here were immensely prolonged. In a third case 100 cc. of fresh blood-mixture were substituted for the poisoned fluid. This should have been more effectual, but, though faint recovery occurred at the end of one revolution, the recovery was not good even after three rounds, about thirty minutes.

Ethyl Alcohol, C^2H_6O.

	1° of Room.	Quantity.
Nov. 15	13° C.	6·8 cc.
,,	15° C.	6·4 cc.
Nov. 16	14° C.	6·8 cc.
,,	15° C.	6·4 cc.
Nov. 17	15° C.	7·2 cc.
,,	15° C.	6·8 cc.
		40·4 cc. ∴ Ai. = 6·73 cc. = 114 minims.

The heart was arrested in diastole.

As with methylic alcohol there was nothing of note as to the effect on frequency of contraction, except that here too

in the end stages spontaneous action ceased completely, whilst the heart still remained excitable for electric shocks, in a lessening degree, however, the secondary coil of the Du Bois Reymond induction apparatus requiring in some instances to be pushed home.

The breadth of the beat increased in the end stages.

The latent period was not increased in the early stages; in the latter stages it was perhaps a little, but the effect was not pronounced.

The "period of diminished excitability" was shortened.

The effect of continuous faradization was lessened markedly in the end stages.

Dilution of the poisoned fluid with its own bulk (100 cc.) of saline, 0·6 per cent., gave in three cases early and good recovery. Substitution of the poisoned fluid by 100 cc. fresh blood mixture gave similarly early and good recovery. The rate of circulation through the heart was in all these cases very good.

PROPYL ALCOHOL, C^3H_8O.[1]

	t° of Room.	Quantity.
Feb. 14	17°5 C.	3·4 cc.
,,	18° C.	5·2 cc.
Feb. 15	19° C.	3·8 cc.
,,	19°5 C.	3·6 cc.
Feb. 17	18° C.	2·6 cc.
,,	18° C.	2·8 cc.

21·4 cc. ∴ Av. = 3·5 cc. = 59·32 minims.

The heart was arrested in diastole.

The end stages in each case showed absence of spontaneous action; also, in some of the cases in these stages, a markedly diminished susceptibility to respond to stimulation.

The trace broadened out in the later stages, in some cases very considerably, the diastole seemed chiefly affected.

The latent period suffered slight increase.

---

[1] This was the normal alcohol. It was obtained from C. A. F. Kahlbaum of Berlin.

The "period of diminished excitability" was, if anything, slightly shortened.

Simple dilution with 100 cc. saline, 0·6 per cent., gave in four cases good and rapid recovery. The recovery set in in from two to four minutes, and rapidly increased. With the ethyl alcohol the recovery was equally or even more rapid.

In the case of all three alcohols the phenomenon of *piling up* obtained, *i.e.*, at the moment of completed systole it was possible to excite the ventricle to further contraction, this latter starting from the culminating point of the preceding contraction as from a point of rest. This was well seen in the middle stages, when the height of the beat had suffered decided diminution.

The quantitative results obtained in the first series of experiments with the higher terms of the alcohol group will now be given, and the results from the complete series considered together. The numbers represent the quantities in minims.

Primary Butyl Alcohol, $C^5H_{10}O$. (Isobutyl Alcohol.)	Primary Amyl Alcohol, $C^4H_{12}O$. (Amyl Alcohol.)
15·3 minims.	5·95 minims.
17·0 ,,	5·95 ,,
22·1 ,,	6·8 ,,
16·8 ,,	7·8 ,,
15·6 ,,	7·2 ,,
15·5 ,,	6·6 ,,
	5·0 ,,
102·3 ∴ Av. = 17·05 minims.	8·0 ,,
	53·30 ∴ Av. = 6·66 minims.

In addition experiments were made with a *secondary* and a *tertiary* alcohol, viz.:

Pseudo-Propylic Alcohol, C^3H_8O.	Pseudo-Butylic Alcohol, $C^4H_{10}O$.
48·45 minims.	40·8 minims.
39·1 ,,	32·3 ,,
45·9 ,,	30·6 ,,
28·0 ,,	39·1 ,,
49·3 ,,	51·0 ,,
56·1 ,,	49·3 ,,
266·85 ∴ Av. = 44·47 minims.	243·1 ∴ Av. = 40·5 minims.

The examination of the alcohols in the first series of experiments was more with a view to establishing a quantitative relation simply, hence they were not examined with reference to the effect on latent period, "period of diminished excitability," susceptibility to Faradic stimulation, &c., as in the case of the experiments just detailed. Nor were the dilution effects worked out. For quantitative consideration the whole series is certainly available; but qualitatively, beyond the fact that each member caused *diastolic* arrest, the consideration must be limited to the first three members of the series.

Leaving out of consideration for the moment the *secondary* and *tertiary* alcohols last mentioned, the series show the following numbers:—

205·5	114	59·3	17	6·6
Methylic.	Ethylic.	Propylic.	Butylic.	Amylic.
CH_4O	C^2H_6O	C^3H_8O	$C^4H_{10}O$	$C^5H_{12}O$

The first three members are strictly comparable, for they represent the normal alcohols. The last two, though not the normal alcohols, still are *primary* representatives, and hence, chemically, very closely approach the normal; they may therefore stand for comparison with the others. We note, then, first, the rapidly ascending ratio of activity as we pass from the lower and simpler alcohol to the higher and more complex member of the series; hence the first proposition is: *that the activity increases with the complexity.* There can be no doubt on this score; but we note further that the numbers of the first three members stand to each other very nearly indeed in geometric progression. The ethylic number is half the methylic, the propylic half the ethylic. The butylic and amylic numbers do not fit in to the series, it is true; they do not, however, show any falling off in activity but rather an increase; hence it would appear that a difference of CH_2, which is that by which each molecule in the series differs from its preceding and succeeding terms, is capable of halving or doubling, as the case may be, the activity of the molecule, or, indeed, the increase in activity may be even in excess of this ratio. The number of experiments requisite to establish definitely a precise

relationship of molecular structure and physiological activity would have to be very large, in view of the considerable variations which must exist between individual frogs, even during the same season of the year. It is, however, more than probable that some such definite relation as that noted does obtain, and that each "CH_2" may be said, in a way, to have its physiological equivalent. Of course, the probability of the existence of such relationship would not be limited to this one particular series, but would apply to other instances of homologous series; and the proposition would simply be, that so long as you keep the arrangement of your units similar, so long as the lines of your structure remain the same, the addition or subtraction of each unit will carry with it a definite and constant difference. It appears that recently Mr. Perkin has demonstrated as much for certain of the alcohol series, having shown that under certain definite conditions the addition of each CH_2 corresponds to a definite quantitative difference in the degree of polarization of light which the particular alcohol is capable of effecting. This subject is of perhaps more importance than may at first sight appear, and may hence warrant further consideration. These alcohols, confining attention to the normal representatives present us with a series of bodies exactly similar in the *form* of their structure. This is best demonstrated by a consideration of their graphic formulæ, which would stand thus :—

Methylic	$H\begin{pmatrix} C\,O\,H. \\ H_2 \end{pmatrix}$
Ethylic	$H\,C\begin{pmatrix} C\,O\,H. \\ H_2 \end{pmatrix}$
Propylic	$H\,C\,C\begin{pmatrix} C\,O\,H. \\ H_2 \end{pmatrix}$
Butylic	$H\,C\,C\,C\begin{pmatrix} C\,O\,H. \\ H_2 \end{pmatrix}$
Amylic	$H\,C\,C\,C\,C\begin{pmatrix} C\,O\,H. \\ H_2 \end{pmatrix}$

Each term in this series is seen to differ from its preceding term by the group "CH_2," but it will be seen that this addition does not mean derangement; each "CH_2" thus interpolated enters into combinations precisely

similar, and hence it must be apparent that whatever change in properties the addition of the group "CH_2" effects in the first instance, a like change must be effected by the addition of the group "CH_2" in the second instance, and so on. We are indeed simply dealing with a chain of like material and structure but composed of more or fewer links. There is, however, one other point for mention, viz., that such series, whilst it means *quantitative difference*, implies *qualitative likeness.*

The secondary and tertiary alcohols cannot come for comparison into such a series, for the additional "CH_2" interpolated does not now enter precisely similar relations, but comes into relation with the group "$\overset{H_2}{C}OH$," placed in brackets above, and so modifies the general structure.

Similarly, the isoprimary alcohols do not strictly fit into the above series; but the additional "CH_2" groups do not modify the arrangement of the group "$\overset{H_2}{C}OH$," which we are taught by chemists is the more important group in the alcohol molecule; hence these *primary* isomerics showing much smaller differences may, without much stretch, be used for comparison.

Returning to the results of our experiments with the first three members we note that *qualitatively* there is agreement on most points. Thus, all three arrest the heart in diastole; in the later stages of toxic action the spontaneous beats are inhibited, and electric excitability is apparently somewhat lessened; the excitability for continuous faradization lessens; the "period of diminished excitability" is shortened. All three show the phenomenon of "piling up."

The primary butylic and amylic alcohols were not examined on all these various points, but they arrest the heart in diastole and they show the "piling up" just noted. We may take it, however, that the first three demonstrate sufficiently *qualitative likeness.*

The heart, we have said, is arrested in diastole; from an examination of the charts no distinct evidence of a primary

stimulation in the shape of increased frequence was determinable. In the case of ethylic and propylic alcohols there did appear to be some quickening, but with the butylic and amylic members the tendency appeared to be rather the other way. There was no primary increase in the height of the trace, the amplitude diminished steadily from the beginning. This last point was tested specially in the case of ethylic alcohol—firstly, by allowing the ventricle to become fatigued before adding the drug; and secondly, by increasing before addition the internal pressure by raising the head of pressure; in either case the ventricle at the moment of administration of the drug was emptying itself *in*completely, but in neither case did the contractions become more complete. These experiments, therefore, will not account for the clinical evidence as to the primary effect on the force of the heart's contractions, but show rather that such effect is not the result of direct action on the cardiac tissues. They are, however, quite in accordance with the enfeebled condition of the circulatory apparatus in the later stages of alcohol narcosis, and show that the direct action of the drug on the tissues tends to bring about this state.

To sum up, these experiments demonstrate more definitely than experiments on the whole organism could—

(1) The *qualitative similarity* of action of the different members of the alcoholic series.

(2) The *general quantitative relationship*, viz., that as the complexity of the molecule increases the physiological activity increases.

(3) The probability of a *further quantitative relationship*, viz., that the constant chemical difference is corresponded to by a constant physiological difference—that each "CH_2" group increases the activity by a *definite* amount.

The third proposition obviously suggests that such relationship is to a like degree probable for other homologous series of bodies.

In addition to these results we must not forget the practical value of experiments which show, as tested by one particular tissue, a relative activity of 114 : 6·5 for ethylic

and amylic alcohols, the more so that this particular amylic alcohol examined is the alcohol of fermentation and that which contaminates our alcoholic preparations. The butylic alcohol examined is likewise the fermentation and contaminating product. We may take it then as settled, that these higher alcohols are far more poisonous, though indeed the balance of opinion was already to this effect. The only remaining point to be noted is that by their direct action on the cardiac tissues these drugs are clearly paralysant, and that this appears to be the case from the outset, no stage of increased force of contraction preceding.

An Investigation regarding the Action of Strontium and Barium Salts compared with the Action of Lime on the Ventricle of the Frog's Heart.

By SYDNEY RINGER, M.D.
AND
HARRINGTON SAINSBURY, M.D., M.R.C.P.

[From the *Practitioner*. Vol. xxxi., page 81.]

THESE investigations were made to ascertain how far the chemical similarity between lime, strontium, and barium indicates a similarity in their physiological and, therefore, in their therapeutic action. Theoretically, we may say, if these substances are physiologically allied, we should expect to find that, as strontium is chemically more akin to lime than barium is, strontium in its physiological action ought to show a greater relationship to lime than barium shows to lime.

In testing the action of any substance on a tissue, as, for instance, the ventricle of the heart, the substance must be mixed with as simple a fluid as possible. If the substance in question is brought in contact with a complex fluid, like the blood, one of the constituents of this fluid may completely antagonise some of its effects. For instance, lime salts, when added to a saline solution, at first broaden the beat and later on greatly prolong dilatation, but a physiological dose of potassium salt will nullify these effects, so that, no matter how much of the calcium salt is added to the circulating fluid, it is impossible to reproduce either the broadening of the beat or the prolonged dilatation.

In testing how far strontium and barium affect the ven-

tricle like calcium, we made a series of experiments with strontium and barium, similar to a series made some months ago with calcium salts, and published in the *Journal of Physiology*. We studied separately the action of the barium and strontium salts when added to simple saline solution. On the result so produced we then tried the modifying action of a potassium salt; next we tried the effect of a mixture consisting of saline solution, a calcium salt, and potassium chloride; and then the effect of a mixture consisting of saline solution containing a lime salt and potassium chloride and sodium bicarbonate.

In these experiments we used Roy's tonometer, by means of which fluid is made to circulate through the ventricle attached to a double cannula. The ventricle is inclosed in a glass vessel with a membranous diaphragm, which moves with each contraction of the ventricle, and by means of a lever the movement, greatly magnified, is recorded on a revolving cylinder.

These investigations were made in January and February.

The blood-mixture employed in these experiments was made by dissolving dried bullock's blood so as to represent normal blood, and this was diluted with two parts of saline, made with tap-water containing a minute trace of lime.

The saline solution contained 0·75 per cent. of pure sodium chloride.

The ventricle was tied on the cannula as near as possible in the auricula-ventricular groove.

We first give a brief account of the effect of lime salts so that we may compare their behaviour with the behaviour of strontium and barium salts :—

A lime salt, as the bicarbonate or chloride, when added to saline solution, broadens the trace of each contraction and rounds its top; it soon delays dilatation, and if the contractions retain normal frequency then, owing to this increased duration of each contraction, much fusion of the beats ensues with some persistent spasm.

A physiological quantity of potassium chloride will remove all these effects.

With saline solution and calcium chloride, after half an hour to three-quarters of an hour, the contractility of the ventricle grows less and eventually ceases, but the addition of a little sodium bicarbonate restores good contractions, though the trace is very rounded and much fusion ensues.

Without the presence of a lime salt in the circulating fluid the contractility of the cardiac muscle cannot, we find, be sustained; with any combination of the salts in the blood without lime the contractility, whether spontaneous or from artificial excitations, soon diminishes and disappears; further, a potassium salt, we find, is also necessary, for with saline solution and a calcium salt the contractility disappears in an hour, but will persist much longer if a physiological quantity of potassium chloride is present. Moreover, if the solution is neutral, though it contains sodium chloride, potassium chloride and calcium chloride in the right proportions, yet in about an hour and a half the spontaneous or induced contractions begin to grow weak; but we find that this diminished contractility is at once obviated by adding to the circulating fluid an alkaline solution, which, we suggest, neutralises the acid developed in the cardiac muscle, which acid is probably the cause of the weakening of the contractions.

An efficient circulating fluid for the maintenance of the heart's contractility must therefore be slightly alkaline in reaction, and must contain, besides sodium chloride, a due proportion of lime and potassium salts.

Chloride of strontium behaves much like chloride of calcium, to which it is so closely allied chemically.

When 2 to 4 cc. of a 1 per cent. solution of strontium chloride is added to 100 cc. of saline, then, as with lime salts, the trace becomes much broader and the top much rounder, with acceleration of the spontaneous beats. Hence fusion ensues, and in addition there is some tonic contraction (contracture). When the ventricle beats unfrequently enough to prevent fusion, then decided delay in dilatation takes place. In from twenty to thirty minutes the contractions grow very weak, or contractility may be lost and contracture disappear, so that the trace recovers

its early position to the base line. Then, on adding 4 to 5 cc. of a 1 per cent. solution of sodium bicarbonate to 100 cc. of the saline and strontium solution, as is the case with lime, spontaneous contraction, or contractility on stimulation, returns, but the trace becomes even broader than with saline and strontium alone, so that fusion again takes place, also accompanied with some contracture.

So far, then, strontium salts differ from calcium salts only in one respect—strontium salts accelerate the beats whilst lime salts tend rather to retard them.

As with lime so with strontium—a small quantity of potassium chloride obviates the effect of strontium, diminishing the frequency of the beats, lessening their duration, removing contracture, and accelerating dilatation. Potassium chloride acts in the same manner when the contractions, grown weak with saline and strontium, have been strengthened by adding sodium bicarbonate.

If potassium chloride is added to the circulating fluid in quantity only just adequate to moderate but not to remove the influence of the strontium,[1] the trace then becomes greatly prolonged, in a far greater degree than I have ever seen lime produce. Diastolic dilatation is delayed, and often in the middle a kind of brief arrest takes place, or even an abortive contraction. This again I have never seen occur with lime.

The contractility of a ventricle fed with 0·75 per cent. solution of sodium chloride quickly declines and then spontaneously recovers to a great extent, or even completely; but in about twenty to thirty minutes it disappears. A suitable dose of a lime salt, as, for instance, calcium chloride, prevents the primary weakening and sustains contractility longer than with saline solution alone. Moreover, when with saline solution contractility has ceased, it returns and becomes good on the addition of a lime salt to the circulating fluid.

---

[1] As, for instance, in the following combination : 100 cc. saline, 1 cc. of a 1 per cent. solution of potassium chloride and 2 cc. of a 1 per cent. solution of calcium chloride.

In both respects the action of strontium chloride is similar to the action of calcium chloride.

Like lime, strontium constitutes a good circulating fluid. We replaced blood-mixture with a solution consisting of 100 cc. of saline solution, 4·5 cc. of a 1 per cent. solution of chloride of strontium, 6 cc. of a 1 per cent. solution of sodium bicarbonate, and 1 cc. of a 1 per cent. solution of potassium chloride, and ninety minutes after the substitution the ventricle beat nearly as well, and the contractions remained of the same character, as with blood-mixture.

We see, then, that strontium in almost all respects behaves like lime. It accelerates the beats more than lime ; it also prolongs dilatation more. In all other respects lime and strontium agree in their action on the ventricle.

We next performed a similar series of experiments, with barium chloride, to the series just described with strontium.

We first tested the action of barium chloride added to saline solution. After taking a trace with blood-mixture, we replaced it by 100 cc. of saline solution containing 1 cc. to 2 cc. of a 1 per cent. solution of barium chloride.

Barium chloride prevents the great early weakening of the ventricle which ensues when simple saline solution is used to replace blood-mixture. In a ventricle not beating spontaneously it produces frequent spontaneous contractions, and in a ventricle beating spontaneously but unfrequently it increases the frequency of the contractions. It also broadens the beat, and this, with the great frequency of the contractions, causes fusion, with the induction of almost complete tetanus, even by small doses. Barium chloride also induces persistent spasm.

In most of these effects barium is like calcium and strontium, except that it accelerates the beats more than strontium, whilst calcium chloride often diminishes their frequency.

Potassium chloride obviates the prolonged dilatation induced by lime or strontium, and this is the case, too, with barium in small doses. Indeed, we get three different effects with potassium chloride, according to the quantity of barium chloride. With a small dose, as, for instance,

2 cc. of a 1 per cent. solution in 100 cc. of saline, 1 cc. of a 1 per cent. solution of potassium chloride entirely removes the contracture, the fusion of the beats, and the prolongation of diastolic dilatation.

With larger doses of barium chloride, potassium chloride (1 cc. of a 1 per cent. to the 100 cc. saline) removes contracture, prevents fusion by lessening the frequency of the beats, though dilatation is still much retarded, and for a short time even undergoes arrest; and during this arrest a partial contraction occurs, or even several, and then dilatation becomes complete. The contractions then grow weaker till contractility ceases.

After a large dose of barium chloride, as 1 cc. of 10 per cent. solution in 100 cc. saline, potassium chloride is unable to antagonise the barium effects, almost complete fusion persisting after the addition in successive doses of 5·5 cc. potassium chloride 1 per cent. solution. Sodium bicarbonate added (5 cc. 1 per cent. solution in 100) only made the fusion more complete, whilst the further addition of 10 cc. of a 0·5 per cent. solution of calcium chloride produced a marked effect. The fusion gradually diminished, and the trace gradually fell, till it occupied its original position, to the base line, and at last normal regular contractions ensued of the same character as at the beginning of the experiment, though the contractions were weaker, the trace being only half as high as that given with blood-mixture.

In this experiment, then, lime removed the effect of barium, and restored fair natural contractions. Calcium, therefore, has a stronger action in the ventricle than barium, unless barium is used in large quantities.

As with lime so with barium, when the ventricle, supplied first with saline and barium chloride, and then with potassium chloride, grows weak or stops, the addition of sodium bicarbonate improves or restores the beats. Thus we replaced blood-mixture by 200 cc. of saline containing 2 cc. of a 1 per cent. solution of barium chloride. The contractions at first became very irregular, then more regular, and then fusion and tetanus ensued.

We then added some potassium chloride and the fusion ceased, but prolonged dilatation remained, and the contractions grew very weak, but on adding sodium bicarbonate they improved, though the prolonged dilatation continued. On the addition of calcium chloride the beats greatly improved, and became of the same character as the beats produced with blood-mixture, *i.e.*, the lime removed the barium effects.

With lime or strontium salts added to saline solution containing a small quantity of potassium chloride, contractility persists for an hour or two, and much longer if the circulating fluid contains a small quantity of sodium bicarbonate. Indeed, a good artificial circulating fluid can be made with either calcium chloride or strontium chloride with saline solution containing potassium chloride and sodium bicarbonate.

This, however, is not the case with barium chloride, for numerous experiments show that with small doses of barium chloride the ventricle grows quickly weak and contractility soon ceases; whilst with larger doses fusion and contracture occur, so that the ventricle speedily passes into tetanus, and this fusion and contracture is not to be obviated by increasing the quantity of potassium chloride.

Indeed, numerous experiments show that it is impossible with barium to form a fluid capable of sustaining the contractility of the ventricle. Thus barium in this respect differs in its action from lime and strontium.

The difference between calcium chloride and strontium chloride on the one hand and barium chloride on the other is well shown in the following experiments, which we have many times repeated:—If 2 cc. of a 1 per cent. solution of barium chloride is added to 100 cc. of saline containing potassium chloride and sodium bicarbonate in appropriate proportions, the ventricle, through fusion and contracture, passes into tetanus; but then the addition of calcium chloride or strontium chloride to the solution entirely removes the barium effects, the fusion and contracture disappear, and good normal beats return, equal to the beats produced with blood-mixture.

Calcium chloride antagonises and suspends the effect of barium chloride; but an additional quantity of barium chloride overcomes the calcium chloride and barium effects reappear, but a further dose of calcium chloride again removes these barium effects, and so on, as we exemplify in the following experiment :—

First we took a blood-trace, and then replaced the blood by 200 cc. of saline containing 4 cc. of a 1 per cent. solution of barium chloride. The barium soon broadened the beat, increased the frequency of the contraction, and caused considerable fusion of the beats. We then added 1·5 cc. of a 1 per cent. solution of potassium chloride. This brought the trace down to its old position on the base line. Then we added some calcium chloride and only slightly improved the strength of the beat, which, however, became much stronger on the addition of sodium bicarbonate. The beats, however, were exceedingly irregular, but a further dose of calcium made them good and regular. Then we added some barium chloride to the circulating fluid (6 cc. 1 per cent. in 100), and the contractions soon became much more frequent and far weaker. We then added 8 cc. of calcium chloride, $\frac{1}{2}$ per cent. solution in 100 cc., and the beats became rather less frequent and much stronger. The addition of some more barium chloride again increased the frequency and diminished the amount of contraction, which once more improved on adding some more calcium chloride to the circulating fluid.

We next experimented to ascertain whether the calcium chloride molecule or the barium chloride molecule has the greater affinity for the ventricle. We used solutions calculated according to the molecular weights of these substances, so that in the same quantity of either solution we employed an identical number of molecules of each substance.

We added 1 cc. of a 2·08 per cent. solution of barium chloride to 200 cc. of saline, which produced acceleration of the beats with considerable fusion and contracture. We then added 1 cc. of a 1·1 per cent. solution of calcium chloride. This removed the barium effects, at least to the

extent of suppressing the fusion and contracture. On adding another cubic centimetre of barium chloride solution, the fusion and contracture reappeared.

We again tested the effect of lime in antagonising barium. We replaced blood-mixture by 200 cc. of saline solution containing 2 cc. of a 2·08 per cent. solution of barium chloride, and 2 cc. of a 1 per cent. solution of potassium chloride. This quantity of potassium chloride is ineffectual to antagonise the effects of the dose of barium chloride, and consequently the contractions soon became spontaneous and frequent, with much fusion and contracture. Then we added 2 cc. of a 1·1 per cent. solution of calcium chloride, with speedy disappearance of the fusion and the contracture, the spontaneous beats ceased, and on excitation beats were induced very similar to those produced with blood-mixture.

Here, then, lime replaced the barium, whilst the potassium chloride, though unable to antagonise the fusion and contracture produced by the barium, yet obviated the effect of calcium on diastolic dilatation, hence the production of a normal blood-beat.

On another occasion we tested, in the way to be described, the antagonism between calcium and barium :—

We tested the action of pure saline; of 200 cc. of saline containing 1 cc. of a 2·08 per cent. solution of barium chloride ; of 200 cc. of saline containing 1 cc. of a 1·1 per cent. of calcium chloride and 1 cc. of a 2·08 per cent. solution of barium chloride ; and 200 cc. of saline containing 1 cc. of a 1·1 per cent. solution of calcium chloride.

The barium solution produced a very marked effect on the ventricular contraction, greatly accelerating and broadening it, and effecting almost complete fusion.

The lime solution produced very little more effect than simple saline solution ; the trace became a little broad, the beats did not fuse, and the dilatation was a little more prolonged than with saline solution alone. The effects of the lime, compared with the marked effect of barium, were very slight. Barium chloride and calcium chloride solution, containing the same number of atoms of each element,

affected the trace much less than barium chloride simply, but in a greater degree than calcium chloride. The beats were accelerated and broadened, but not enough to produce fusion. Calcium, then, much antagonised the effect of barium.

Barium and calcium, as we have pointed out, have many actions in common. Both cause fusion and contracture, but barium in a greater degree than calcium. If both simultaneously operated on the heart, then, as potassium chloride is singly unable to remove the effects of barium, still more so should it be impotent to antagonise the joint action of barium and calcium ; but we have seen that on the addition of calcium chloride to saline solution containing barium chloride and potassium chloride that fusion and contracture disappear, and the trace becomes like a blood-trace. The lime replaces the barium, and the potassium chloride is effectual in preventing the delay in dilatation, which lime, unantagonised by potassium, produces. The molecule of lime chloride, therefore, has a stronger affinity for the cardiac structures than the molecule of barium chloride.

It is interesting to observe that, although lime salts and barium salts both broaden the beat, causing fusion and producing contracture, barium salts effecting this more powerfully than calcium salts, yet when both a barium salt and a calcium salt are added to the circulating saline, the one does not increase the effects of the other, but lime takes possession of the muscular tissue, excluding the action of the barium salt.

It would seem, then, that two substances affecting the same tissue in the same way when administered therapeutically, one will not intensify the action of the other but will replace the other, and we get mainly the action of only one of the substances. But although a molecule of calcium chloride will overcome and exclude the action of a molecule of barium chloride, yet by increasing the relative number of barium chloride molecules we can overcome the chloride of calcium action.

Next we sought to ascertain whether a lime salt or a

barium salt, molecule for molecule, produces the greater amount of functional alteration in the cardiac structures.

In these experiments the chloride of calcium solution contained 1·1 per cent. of the salt, and the chloride of barium 2·08 per cent. of the salt, both being calculated irrespective of the water of crystallisation, which was carefully driven off by heat. We find that 1 cc. of the calcium chloride solution in 400 cc. of saline produces scarcely any effect on the ventricle, whilst 1 cc. of barium chloride in 800 cc. of saline produced decided barium effects. Hence, molecule for molecule, barium induces greater functional changes than lime, although lime has a greater affinity for the cardiac structures than barium.

Examined as to their individual action, the previous experiments have shown that a considerable similarity exists between the chlorides of calcium, strontium, and barium. This corresponds, we know, to a considerable similarity which chemically obtains for these three elements. We have further seen that physiologically the above salts contrast in respect of intensity of action. Thus, taking the extremes, we have seen that, molecule for molecule, barium chloride causes more functional disturbance than calcium chloride. This difference is marked and holds even for equal weights of the two salts, in which case we have just about half as many molecules of barium as of calcium chloride. This functional difference has again a corresponding chemical difference, for chemically the energy and basicity increase with the atomic weight, and barium stands as a considerably more energetic element than calcium.

A more complex problem appears when we come to consider the simultaneous action of two or more of the above salts. The results obtained are very interesting, and have considerable importance physiologically. Thus we have seen that barium and calcium both exert an influence in the same direction, but that the barium molecule is the more active. If, however, we bring both molecules into action simultaneously, we note that the resultant effect, instead of being greater than either component, is intermediate in its position, being greater than the calcium,

but less than the barium effects. Instead of a summation we have to record an interference; the action of the one molecule clashes more or less with that of the other molecule. The importance of this subject in relation to practical medicine, is very clear, for on the question of the combination of medicines we shall have to remember that the joint action of two drugs, functionally similar, is not necessarily greater than that of either separately. We shall have, of course, to remember that our very broad lines of classification into purgatives, astringents, &c., include agents most dissimilar in action, and shall not conclude that because practically a combination of aloes and colocynth, or of cassia-pulp and manna, is found more effective than either agent separately, that therefore interference (antagonism) cannot obtain between drugs having similar qualities. The doctrine of antagonism is a most important one, but as a rule we are accustomed to consider this as relating to agencies opposed in their quality of action. The above experiments however prove that it may apply also to the actions of similars. The explanation of this antagnonism of barium and calcium chloride is not very apparent, for, if we regard it as a case of displacement of the former by the latter, we meet with an apparent discrepancy in the fact that an element chemically more energetic and physiologically also more active, as experiments with the barium and calcium chlorides separately teach, in the fact that such should be turned out by a weaker element. Nor, indeed, would simple displacement account for all the facts of the case, for in the experiment in which an equal number of molecules of barium and calcium chloride were first tried singly and then jointly, the result in the latter case was not a simple reduction to the calcium chloride effect, but an effect intermediate between the two. Whatever, then, the explanation may be, the fact of *interference* remains.

There remains another point for discussion. It was noted that after the removal, say, of the barium effect by the calcium salt, the further addition of more of the barium salt brought back the barium effect, to be again removed

by further increasing the dose of calcium. This dominance of action, according as the mass of the one or the other element dominates, is a fact of great importance to the physiologist; it is an example of what chemists term mass action, according to which they teach us that a substance incapable of effecting a decomposition in one proportion may become thus capable by simply increasing the proportion of this substance, all other conditions remaining the same. Thus, for instance, the compound water, which theoretically is a base, but of which quality we get ordinarily no evidence—this same may be made to turn out a far stronger base by increasing enormously the relative proportion of the weaker base, the water, to the stronger base in question. Thus then the simple process of dilution may be made to effect chemical decomposition. This question, whilst individually it puts the substance water in a new light before us, opens up the whole subject of mass action, for, leaving special instances aside, it is clear that, if the chemists be right in their interpretation of the phenomenon, then simple dominance of mass, rather than by how much or how little, is that which concerns us. All degrees may be expected in a scale ranging from bodies so unequally matched that the question of dominance becomes an impracticable one up to those so nearly balanced that a slight preponderance will turn the scale in one or other direction.

It is clear that the problem of estimating the action of a given compound in the presence of other compounds becomes a very complicated one, and increasingly so as the number of elements present increases. Without further speculation on the subject of mass action, we shall have simply to remember that mass is an element in the problem, and the physiologist, dealing as he does with substances for the most part in great dilution, will have to bear in mind that under these conditions even water may become a factor of importance, instead of being the simple vehicle we have been accustomed to consider it.

However theoretical these points may at first sight appear, none could well be more practical if we are to advance

from an empirical to a rational administration and combination of drugs. In a previous series of experiments we have seen that in the action of certain salts on the tissues, the question of percentage strength, rather than the actual quantity of the salt present, determines the effect, and that, after the percentage strength has reached a poisonous degree, the functions of the tissues may be restored by simple dilution. These effects, as has been already pointed out, indicate that the changes effected in the tissues by such salts cannot be very profound, nor the compounds formed very stable. It is possible that these phenomena may find their explanation in the mass action just considered, and that the water in these instances may be considered active rather than passive. As the matter at present stands, it is of little importance how the phenomena are named, but we must not forget that, in the chemistry of the tissues, interference or antagonism obtains even between salts similar in their action, and that the mass of the salt present is an element requiring consideration.

An Experimental Investigation to Ascertain in what manner Soluble Oxalates Arrest Function, and Some Remarks on the Action of Poisons and their Antidotes.

By Sydney Ringer, M.D.

[From the *Practitioner*. Vol. xxiv., page 81.]

Soluble oxalates are strong and speedy poisons, and in these investigations I have endeavoured to ascertain in what manner they arrest function and destroy life.

I have elsewhere shown that a lime salt must be present in the circulation to sustain the contractility of the cardiac muscular tissue. Lacking lime,[1] any combination of the other inorganic substances occurring in the blood is insufficient to maintain the heart's contractility. Even a minute trace of a lime salt, as the bicarbonate, with a physiological quantity of potassium chloride and sodium chloride, will sustain the muscular contractility.

If this holds good in regard to the cardiac muscle, it probably applies to all muscular tissue. Moreover, I venture to suggest it applies also to all the tissues, so that by excluding lime from the circulating fluid it is probable that no function would be possible.

Any substance, therefore, capable of precipitating the

[1] Ludwig, however, finds that the spontaneous contraction of the ventricle will persist for many hours when the ventricle is supplied with the following circulating mixture : sodium chloride, 0·5 per cent. solution, 100 cc. ; caustic potash ·002 grammes, and peptones ·003 grammes.

whole or part of the lime from the blood will suspend or weaken the heart's contractility, and probably the muscular contractility generally, besides other functions, whilst the re-introduction of a lime salt will restore the suspended contractility and the functions in abeyance.

Oxalate of lime is extremely insoluble. It is slightly soluble in saline solutions, and I hope to show that when a soluble oxalate is added to the blood, it precipitates enough lime to weaken the heart's contractility, though enough oxalate of lime remains in solution to sustain weak contractions. I shall show, also, that oxalates are directly poisonous to the cardiac muscular tissue, for enough of them added to the blood will quite suspend the heart's contractility; but at this point the addition of lime renders the oxalates almost entirely insoluble, and contractility returns with the renewal of good contractions, provided enough lime be used to replace that precipitated by the oxalic acid.

The following experiments were made with the detached ventricle of the frog's heart tied on the perfusion cannula of a Roy's tonometer. By means of a syphon action, blood can thus be made to circulate through the detached ventricle, and its contractions are recorded on a revolving cylinder. The circulating fluid was made by dissolving dried bullock's blood in saline solution prepared with water supplied by the New River Company. This water contains a small quantity of carbonate of lime.

I added 1 cc. of 5 per cent. solution of oxalate of ammonia to 100 cc. of circulating blood-mixture. The ventricular contractions at once grew weaker, and contractility tested with strong induction shocks ceased in about sixteen minutes. I then diluted the blood with 100 cc. of saline solution, and in another eight minutes added a second 100 cc. of saline, but contractility failed to return. Then I added 4 cc. of 1 per cent. solution of calcium chloride, and spontaneous contractions speedily returned, and, growing stronger, became as good as at the beginning of the experiment.

On another occasion I suspended the cardiac contracti-

lity by adding 4 cc. of 2 per cent. solution of ammonium oxalate. After an interval of twenty-five minutes I added 6 cc. of 1 per cent. solution of calcium chloride, and good spontaneous contractions quickly returned.

These experiments, then, show—

(1) That oxalate of ammonia suspends the contractility of the cardiac muscle.

(2) That dilution of the circulating fluid will not restore the contractility.

(3) That the addition of a soluble lime salt to the circulation nullifies completely the effect of the oxalate of ammonia, and restores good contractions to the heart.

I then experimented to ascertain whether the suspension of contractility is due to the withdrawal of lime from the circulation, or is due to the poisonous action of oxalic acid on muscular tissue, or to both these causes combined.

I prepared solutions of calcium chloride and ammonium oxalate, calculated on their molecular weights. The calcium chloride solution contained 1·1 per cent., the ammonium oxalate 1·24 per cent.

Mr. Gerrard tested these solutions and found that 1 cc. of the oxalate of ammonium solution did not precipitate quite all the lime from 1 cc. of the lime solution, and that about one minim more of the oxalate of ammonium solution was required to precipitate the whole of the lime.

I then used an artificial circulating fluid, consisting of 200 cc. saline solution (0·75 per cent.), 2 cc. of 1 per cent. solution of sodium bicarbonate, 1.5 cc. of 1 per cent. solution of potassium chloride, and 2 cc. of 1·1 per cent. solution of calcium chloride.

I first took a tracing with blood mixture, and then replaced the blood with the solution just mentioned. After recording the character of the beats for a few minutes, I added 1 cc. of the solution of oxalate of ammonium; this, though it weakened the contractions, did not arrest them. The result of several experiments shows us that the addition of enough oxalate of ammonium solution to combine with the whole of the lime reduces the strength of the contraction by one-third to one-half, and moreover that

this weakening is immediately counteracted by the addition of calcium chloride to the circulating fluid.

It is obvious, therefore, that the saline solution dissolves sufficient oxalate of lime to sustain weak contractions in the cardiac muscle, and as a sufficient dose of ammonium oxalate arrests the ventricular contractions, it follows that oxalic acid exerts a direct poisonous action on the muscular tissue.

The addition of a soluble lime salt to the circulating fluid, sufficient to precipitate the oxalic acid and thus to render the salt innocuous, will, as we have seen, at once counteract the direct effect.

These experiments, then, point to the conclusion that in poisoning by oxalic acid, or by a soluble oxalate, lime does not act as an antidote only in the stomach, but manifests its effects in the blood and tissues, and further, that the addition of a soluble lime salt to the circulation will speedily and fully restore functional activity to a tissue in which function is completely in abeyance. It is obvious that in practice we should employ soluble salts of lime, like the chloride, in preference to the insoluble, and that in great weakness of the heart, transfusion with a fluid containing chloride of calcium might be a life-giving expedient.

I now point out some of the ways by which a substance may prove poisonous, and in which its antidote acts. A substance may destroy function and prove poisonous by withdrawing from the circulation a salt necessary to the carrying on of functional changes. Oxalic acid, we have just seen, greatly weakens the heart's contractions by withdrawing much lime from the blood. The antidote here is obviously lime, to replace that lost to the circulation, and so to enable the muscular tissue to contract. Again, a poison being operative only so long as it remains in solution, we can administer some salt to render the poison insoluble, and therefore harmless. In this manner lime is an antidote to oxalic acid or to any soluble oxalate, even in the blood or tissues, for the oxalate of lime is soluble only to a very minute extent, quite inadequate for the oxalic acid to influence the tissues. Soluble barium salts

are poisonous, and arrest the ventricle in systole. Now I find in experiments with the detached ventricle that the addition to the circulating fluid of a solution of sodium sulphate will precipitate the whole of the barium, and the heart will speedily resume its normal contractility, even though the contractions had been suspended for an hour. The effect of the sodium sulphate is very rapid, and it produces a precipitation not only in the circulating fluid, but likewise in the tissues of the heart itself.

Barium salts, one would think, can prove poisonous only to the tissues at a distance from the digestive canal, after more than enough has been absorbed to combine with the whole of the sulphuric acid in the blood and tissues; and it is possible that part of the action of barium may be due to the withdrawal of sulphuric acid from these tissues. It has been suggested, moreover, that the precipitated barium sulphate may block the blood-vessels and produce embolism.

The foregoing are instances of the effects produced by rendering a substance in the circulation insoluble, and so inoperative. I now give instances of antagonism between substances both remaining in solution in the circulation. I shall first refer to what may be termed a physiological antagonism. The heart's normal action is entirely dependent on an antagonism between the lime and potassium salts in the circulation. Without the presence of a minute quantity of a calcium salt in the circulating fluid, the muscular substance of the heart cannot contract; the calcium salt, however, broadens the beat and greatly delays diastolic dilatation, and to such an extent that, whilst the heart beats with normal frequency, a second contraction would begin long before the cavities had dilated from the preceding contraction; hence the cavities would contain very little blood, and the circulation would become greatly lessened.

Now a potassium salt in physiological quantity antagonises this effect of calcium salts on the dilatation, and, indeed, greatly accelerates it, so that the dilatation is completed before the ensuing contraction begins. Here, then, we have a physiological antagonism affecting only one part

of a function, that is, the relaxation after a muscular contraction, the contraction itself being in no wise affected; but if the quantity of potash salt is increased, then the antagonism involves the contraction likewise, and this diminishes in proportion to the quantity of the potash salt till contraction itself is also prevented.

I next refer to the antagonism of substances acting toxically. Veratria affects the muscular substance of the heart much like lime. It prolongs the duration of the contraction considerably, rounding the top of the trace, and greatly delaying the dilatation following a systole. A dose of potash in excess of the physiological quantity in the blood completely obviates this effect. But the antagonism between veratria and potash is more complete, and extends to the contraction as well as to the relaxation and dilatation of the cardiac muscular tissue.

I added 1 cc. of 0·2 per cent. solution of veratria to 100 cc. of circulating fluid. This produced well-marked characteristic irregularity in the ventricular contraction. I then added 3 cc. of 1 per cent. solution of potassium chloride, and this quite obviated the veratria effects and induced normal contractions. We have here, then, an instance of the circulating fluid containing a poisonous dose of veratria and a dose of potassium chloride greatly in excess of the physiological quantity, and yet, from their mutual antagonism, the ventricle is quite unaffected, and perfect normal beats occur.

I give another still more striking example of antagonism —the poisonous substances remaining in solution. I first took tracings of the ventricle supplied with 200 cc. of circulating fluid. I then added 1 cc. of 0·2 per cent. solution of veratria, which produced a well-marked veratria trace with extreme inco-ordination of the ventricular substance. I then added 5 cc. of 1 per cent. solution of calcium chloride. This almost removed the irregularity, but greatly broadened each beat, causing much fusion of the beats. Another 5 cc. of calcium chloride solution quite removed the irregularity, and still more broadened the trace of each beat. The trace had all the characters

of one produced by a large quantity of lime chloride, and it would appear that the lime obviated most of the veratria effects, replacing the veratria action by its own. I then added 10 cc. of 1 per cent. solution of potassium chloride, and produced an almost natural beat. Here, then, the circulating fluid contained three substances in marked toxic quantities, and yet these so antagonised each other that a normal action of the ventricle ensued.

The preceding are instances of the simultaneous administration of drugs with antagonistic physiological action, in which one drug antagonises the other.

I next come to an antagonism between two substances, which nevertheless affect a tissue in a similar way.

When two substances, each capable of inducing a similar change in a tissue, are both added to the circulation, the result of their conjoint action in one case is an antagonism; and in another case one substance reinforces the other, and their united influence produces an effect greatly in excess of the operation of one substance only.

For instance, lime and barium salts affect the cardiac muscular tissue in much the same way. Both broaden the beat and delay dilatation, but barium salts produce a greater alteration than calcium salts. When a soluble barium salt is added to a simple saline, and this is used as a circulating fluid, well-marked barium effects ensue; if to this is now added an equal molecular quantity of a soluble calcium salt, then, instead of an augmentation of the effects common to both ingredients, we get, indeed, a great diminution of these common effects—the lime seems, in fact, to displace the barium from its combination with the tissues, and consequently the lime effects replace the barium effects.

But in other instances the combined action of the two substances which affect the tissues similarly is greater than that of either substance singly. For instance, lime and veratria, which affect the muscular substance of the ventricle in much the same way, if added to saline solution, and this combination is used as the circulating fluid, the duration of the ventricular contraction and the long delay

in dilatation is far greater than when either substance is used singly.

I venture to offer an explanation of this difference in the conjoint effect of two substances, each of which affects a tissue in a similar manner.

In a molecule some of the elements remain unsaturated, and with these unsaturated elements other substances can unite and in this way modify the constitution of the molecule. If two elements remain unsaturated, one substance may attach itself to one element, and another substance to another element. But it may happen that two substances affecting the molecule can attach themselves only to the same unsaturated element, and the substance having the stronger affinity will displace the weaker. These substances, like calcium and barium, chemically closely allied, will most probably have an affinity for the same element, and the stronger calcium will displace the weaker barium, and therefore this substitution of the effects of one substance for those of another similarly acting agent will be most likely to occur between substances having a close chemical similarity.

Other substances differing, *inter se*, widely in chemical nature will attach themselves to different atoms at the same time, and hence the result on the molecule is the combined influence of both substances, as happens with lime and veratria.

Finally, there is another way by which the poisonous action of some substances may be greatly lessened.

Some substances appear to prevent the changes which take place in the exercise of a function, as, for instance, the contraction of muscle. They do not destroy the structure, they only suspend function, and this power they possess only when the poison reaches a certain percentage of the circulating fluid. If the fluid is diluted, then, the percentage amount becoming less, the poisonous action is greatly reduced. This is the case with most salts, like potassium salts. If sufficient quantity is added to the circulating fluid to arrest the ventricle in systole, on adding to the circulating fluid an equal quantity of saline, function immediately returns with good spontaneous beats.

I have elsewhere drawn attention to this fact, and pointed out that in poisoning by such drugs one obvious way of lessening their poisonous action is to dilute the blood, either by directing the patient to drink freely of a saline fluid, or to inject a saline fluid containing a physiological quantity of a calcium and of a potassium salt into the circulation.

Papers and References in "The Lancet."

YEAR	VOL.	PAGE	
1862	I	173	On the Temperature, Urea, Chloride of Sodium, and Urinary Water in Scarlet Fever; and On a Cycle in Disease and Health.
1864	II	675	Testimonial to Dr. Sydney Ringer, of University College Hospital.
1865	II	429	Review. "The Temperature of the Body as a means of Diagnosis in Phthisis and Tuberculosis."
1865	II	512	University College Hospital: The Thermometer in Acute Disease: Case of Renal Inflammation following Scarlatina; Clinical Remarks.
1865	II	648	University College Hospital: The Thermometer in Specific Fever: Case of Typhoid Fever; Remarks.
1866	II	208	The Influence of Alcohol on the Temperature of Non-Febrile and Febrile Persons.
1866	II	381	University College: Dr. Sydney Ringer's Address.
1869	I	42	Paper No. 1 on The Therapeutic Action of Drugs: Aconite and its Preparations.
1869	I	392	Paper No 2, ditto: Bromide of Potassium; Bromide of Sodium; Bromide of Ammonium.
1869	II	10	Review. Dr. Ringer's Handbook of Therapeutics.
1871	II	752	Ditto.
1873	I	53	Ditto.
1873	I	877	Review. "The Temperature of the Body as a means of Diagnosis and Prognosis in Phthisis."
1873	II	469	Letter by Dr. Ringer on the Accidental Poisoning of Dr. Sharpey; Recovery.
1874	I	264	On Sulphide of Potassium, Sulphide of Sodium, and Sulphide of Calcium.

YEAR	VOL.	PAGE	
1874	II	338	Ipecacuanha Spray in Winter Cough and Bronchitic Asthma.
1874	II	805	Review. A Handbook of Therapeutics.
1875	I	157	On Jaborandi. By Dr. Ringer and Dr. Alfred P. Gould.
1875	II	907	On Gelseminum Sempervirens. By Dr. Ringer and Wm. Murrell, L.R.C.P., M.R.C.S.
1876	I	82	Ditto.
1876	I	124	Ditto. The Influence of Gelseminum on the Frog's Heart.
1876	I	415	Ditto. The Influence of Gelseminum on Respiration.
1876	I	561	Ditto. Ditto.
1876	I	661	Ditto. Action on Man.
1876	I	732	Ditto. Influence on the Eyes.
1876	I	921	Royal Medical and Chirurgical Society: An Abstract of the following Paper by Dr. Ringer was read: "Observations on Box (Buxus Sempervirens), with special reference to the true nature of Tetanus."
1876	II	78	On Gelseminum Sempervirens. Action on the Pupils.
1876	II	569	Ditto. Action on the Circulation.
1877	I	228	A Suggestion concerning the Condition of the Nervous Centres in Migraine, Epilepsy, and other Explosive Neuroses.
1877	I	499	Review. A Handbook of Therapeutics.
1877	II	198	The Action of Muscarin on the Human Body. By Dr. Ringer and E. A. Morshead, M.R.C.S., L.R.C.P.
1877	II	912	On the Use of Physostigma in some Nervous Affections. By Dr. Ringer and Wm. Murrell, M.R.C.P.
1877	II	950	Ditto.
1878	I	858	On Gelseminum Sempervirens. Gelseminum as a Toxicological Agent.
1878	I	892	On Gelseminum Sempervirens.
1878	II	473	Concerning the Influence of Perspiration on the Febrile Temperature.
1879	I	160	Review. A Handbook of Therapeutics.
1879	I	290	The Action of Pituri on Man.
1880	I	360	On Tonga: A Remedy for Neuralgia, used by the Natives of the Fiji Islands. By Dr. Ringer and Wm. Murrell, M.D., M.R.C.P.

YEAR	VOL.	PAGE	
1880	I	407	Review. A Handbook of Therapeutics.
1880	I	795	On the Mydriatic Properties of Homatropin, with an Account of its General Physiological Action. By John Tweedy, F.R.C.S., and Sidney Ringer, M.D.
1880	II	6	On Glycerine in Flatulence, Acidity, and Pyrosis. By Dr. Ringer and Wm. Murrell, M.D.
1882	I	1033	Royal Medical and Chirurgical Society: Abstract from a Paper by Dr. Ringer and Dr. Harrington Sainsbury concerning the Action of Salts of Potash, Soda, and Ammonia on the Frog's Heart.
1882	II	12	Review. A Handbook of Therapeutics.
1882	II	736	On the Action of the Salts of Sodium, Ammonium, and Potassium. By Dr. Ringer and Dr. Harrington Sainsbury.
1883	I	7	On Manganese in the Treatment of Amenorrhœa. By Dr. Ringer and Dr. Wm. Murrell, M.R.C.P.
1883	I	87	Letter by "Sceptic" criticizing The Paper on Manganese in the Treatment of Amenorrhœa, by Dr. Ringer and Dr. Murrell.
1883	I	628	Concerning the Effects of Dilution and Concentration on the Actions of Poisons.
1883	II	766	Article on Nitrite of Sodium as a Toxic Agent. By Dr. Sydney Ringer and Dr. Wm. Murrell.
1883	II	880	Letter by Dr. Ringer in reply to Dr. Murrell's explanatory Letter on "Nitrite of Sodium as a Toxic Agent."
1883	II	996	Review. A Handbook of Therapeutics.
1884	II	767	Article on the Nervous or Muscular Origin of certain Spastic Conditions of the Voluntary Muscles. By Dr. Sydney Ringer and Dr. Harrington Sainsbury.
1884	II	815	Ditto.
1884	II	860	Ditto. Conclusion.
1885	I	6	Article on an Examination of the Supposed Action exerted by the Antagonism between Acids and Alkalies in modifying the Tonicity of the Heart and Arteries. By Dr. Sydney Ringer and Dr. Dudley Buxton.
1886	I	792	Review. A Handbook of Therapeutics.
1888	II	1082	Annotation. "Ringer's Therapeutics: Strange Advice."

YEAR	VOL.	PAGE	
1889	I	227	Review. A Handbook of Therapeutics.
1891	II	1212	Article on Pulsations and Murmurs in the Great Veins of the Neck ; their Physiological and Clinical Significance. By Dr. Ringer and Dr. Harrington Sainsbury.
1891	II	1268	Ditto.
1892	I	740	Ditto.
1892	I	790	Ditto. Conclusion.
1894	I	325	Article on "Some Practical Points concerning the Diagnosis of Cardiac Murmurs." By Dr. Sydney Ringer and Dr. Arthur Phear.
1894	II	482	Review. A Handbook of Therapeutics.
1894	II	729	Article on "The Clinical Significance of Accentuated Second Sound." By Dr. Ringer and Dr. Arthur G. Phear.
1896	I	166	Clinical Society of London : Dr. Ringer and Dr. Arthur Phear contributed an Account of a Case of Addison's Disease treated with Suprarenal Extract.
1905	I	582	Reference to Dr. Ringer in a leading article on "Shifting Dullness in the Thorax and Abdomen."
1910	II	1386	Obituary Notice.

Papers and References in "The British Medical Journal."

YEAR	VOL.	PAGE	
1859	—	680	Royal Medical and Chirurgical Society : An Abstract of a Paper by Dr. Ringer on "The Connection between the Heat of the Body and Excreted Amounts of Urea, Chloride of Sodium and the Urinary Water, during a Fit of Ague."
1860	—	654	Royal Medical and Chirurgical Society : Paper by Dr. Ringer on "The Relative Amount of Sugar and Urea in the Urine of Diabetes Mellitus." Communicated by Mr. Richard Quain, F.R.S.
1861	I	343	Note *re* a Paper by Dr. Ringer, in the Edinburgh Medical Journal of February, 1861.
1862	I	211	Royal Medical and Chirurgical Society : Paper by Dr. Ringer on "The Temperature, Urea, Chloride of Sodium and Urinary Water in Scarlet Fever and on a Cycle in Disease and Health." Communicated by A. B. Garrod, M.D., F.R.S.
1865	I	248	Review. "On the Temperature of the Body as a Means of Diagnosis in Phthisis and Tuberculosis." By Dr. Ringer.
1866	II	289	Royal Medical and Chirurgical Society : "The Influence of Alcohol on the Temperature of Non-Febrile and Febrile Persons. By Dr. Ringer and Walter Rickards, M.D.
1869	II	269	Review. "A Handbook of Therapeutics." By Dr. Ringer.
1874	II	288	On the Action of Croton-Chloral Hydrate in Certain Forms of Megrim. (Abstract : Proceedings of Section of Medicine, Annual Meeting, British Medical Association, Norwich).
1874	II	637	Paper in full.
1875	I	380	On the Value of Tar in Bronchial Catarrh and Winter Cough. By Dr. Ringer and W. M. Murrell, L.R.C.P., M.R.C.S.

YEAR	VOL.	PAGE	
1875	I	543	"On Jaborandi."
1875	II	425	A Case of Rheumatic Hyperpyrexia cured by one Cold Bath.
1875	II	775	"A Case of Diabetes Insipidus treated by (1) Jaborandi and (2) Ergot."
1881	I	159	University College Hospital: "A Case of Delirium in Acute Rheumatism under the care of Dr. Ringer. Reported by Mr. David Collingwood.
1882	I	539	University College Hospital: "A Case of Epithelioma of Œsophagus under the care of Dr. Ringer." Reported by Mr. S. H. Collins.
1882	I	943	Royal Medical and Chirurgical Society: "The Action of Salts of Potash, Soda and Ammonia on the Frog's Heart." By Dr. Ringer and Dr. Harrington Sainsbury.
1882	II	1134	"Action of the Element Arsenic." By Dr. Ringer and Dr. Harrington Sainsbury.
1882	II	1193	Continued.
1883	I	451	"An Experimental Investigation of the Action of Chloral, Opium and Bromide of Potassium." By Dr. Ringer and Dr. Harrington Sainsbury.
1883	I	556	Continued.
1883	II	265	"Investigations into the Physiological Action of Barium Chloride." By Dr. Ringer and Dr. Harrington Sainsbury.
1883	II	925	Review. "A Handbook of Therapeutics." By Dr. Ringer.
1883	II	1070	Royal Medical and Chirurgical Society: "Investigations into the Action of the Digitalis Group."
1884	I	97	"Note on some Experiments with Ergotine." By Dr. Ringer and Dr. Harrington Sainsbury.
1884	II	114	Report on the Influence of Rhombic Sodium Phosphate and Sodium Bicarbonate on Muscular Contraction.
1885	I	731	Regarding the Effect of the Saline Ingredients of the Blood on the Contractions of the Heart.
1886	I	303	Review. "A Handbook of Therapeutics." By Dr. Ringer.

YEAR	VOL.	PAGE	
1887	II	1033	Address to the Midland Medical Society : "The Antagonism of Drugs."
1888	I	1257	"Remarks on Paroxysmal Sneezing." By Dr. Ringer and Dr. Murrell. Part I.
1888	I	1327	Part II.
1889	I	139	Review. "A Handbook of Therapeutics." By Dr. Ringer.
1894	II	1499	University College Hospital : Notes on the Antitoxin Treatment of Diphtheria, under the care of Dr. Ringer. Reported by Mr. F. Travers.
1895	II	1412	"Preparation of Milk for Diabetic Patients."
1895	II	1524	Letter by Dr. Ringer on "Preparation of Milk for Diabetic Patients."
1896	I	150	Clinical Society of London : "Addison's Disease treated with Suprarenal Extract." By Dr. Ringer and Dr. Arthur Phear.
1896	II	195	University College Hospital : Case of Antifebrin Poisoning, under the care of Dr. Ringer. Reported by Dr. Alfred Dimsey.
1896	II	1543	Letter by Dr. Ringer on "Belladonna in Bronchitis."
1898	I	701	Review. "A Handbook of Therapeutics." By Dr. Ringer.
1901	I	398	Royal Medical and Chirurgical Society : Remarks by Dr. Ringer during a discussion on "The Outbreaks of Arsenical Poisoning in Beer Drinkers."
1910	II	1276	Formal Note announcing the Death of Dr. Ringer.
1910	II	1384	Obituary Notice.

15/10/95